CLINICAL STUDY REPORT

EFFICACY AND SAFETY ASSESSMENTS OF A PERITONEAL DIALYSIS SOLUTION CONTAINING GLUCOSE, XYLITOL AND L-CARNITINE COMPARED TO STANDARD PD SOLUTIONS IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD)

Sponsor:	Iperboreal Pharma Via L'Aquila 9, 65121 Pescara ITALY
Test Drug:	XyloCore Bags for peritoneal dialysis containing Glucose 0.5%, Xylitol 1.5% and L-Carnitine 0.02% for nocturnal exchanges and Glucose 0.5%, Xylitol 0.7% and L-Carnitine 0.02% for diurnal exchanges
Investigated Indication:	XyloCore is indicated for peritoneal dialysis in patients with chronic kidney failure
Protocol Number:	IP 001-09
Eudract number:	2009-016801-40
Phase:	II
Study Initiation / Completion Dates:	16-10-2019 – 15-2-2022
Coordinating Principal Investigator:	Prof. Mario Bonomini, M.D., Ph.D. "Università degli Studi "G. D'Annunzio" di Chieti Istituto di Clinica Nefrologica Ospedale Clinicizzato "SS. Annunziata", Chieti, Italy Phone: +39-0871 358658/669/634
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Contract Research Organisation:	Sintesi Research S.r.l., Via Privata delle Stelline 9 20146 Milano, Italy
Report Date:	24 January 2024

GCP COMPLIANCE: This study was conducted in compliance with Good Clinical Practices, including the archiving of essential documents.

1. SIGNATURES PAGE:

Clinical Study Report approved by

Dr Arduino Arduini Iperboreal Pharma (Sponsor), Via L'Aquila 9, 65121 Pescara, Italy *CEO and Responsible for Clinical Research*	Date: February 6, 2024
Prof. Mario Bonomini Coordinating Principal Investigator Ss. Annunziata Hospital / Università degli Studi G. D'Annunzio, Via dei Vestini, 66100 Chieti, Italy *Prof. and Head of Nephrology*	Date: February 8, 2024
Dr. Antonio Colantoni Sintesi Research (CRO), via delle stelline 9, 20146 Milano, Italy *Statistician*	Date: 08 FEB 2024

2. SYNOPSIS

Name of Sponsor/Company: Iperboreal Pharma	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
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TITLE OF STUDY: Efficacy and safety assessments of a peritoneal dialysis solution containing Glucose, Xylitol and L-Carnitine compared to standard PD solutions in Continuous Ambulatory Peritoneal Dialysis (CAPD).

INVESTIGATOR(S) AND STUDY CENTER(S): Multicentre; a list of participating investigators is presented in Appendix 16.1.4.

STUDY DATES: Study initiation date:16-10-2019 - Study completion date: 15-2-2022

PHASE OF DEVELOPMENT: Phase II

OBJECTIVES:

Primary Objectives

To assess the safety and tolerability of the experimental solutions by:

- recording the incidence and severity of adverse events;
- recording a subjective questionnaire on the patient's perception of well-being;
- monitoring the changes in routine blood biochemical and hematological parameters.

Secondary Objectives

1. To assess the effects of experimental solutions
   - peritoneal clearances;
   - peritoneal transport characteristics with respect to Day 0 and the follow-up period
2. To assess the effects of experimental solutions on peritoneum functionality by evaluation of changes in CA^{125} and protein levels in ultrafiltrate

METHODOLOGY:

This was a phase II, prospective, investigational, open, multi-center study. The study enrolled stable, End-Stage Renal Disease (ESRD) patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) without major cardiovascular comorbidities, regularly treated for at least three months before selection with a standard solution containing 2.5% of glucose for the nocturnal dwell or regularly treated for at least one month before selection with 1, 2 or 3 diurnal exchange bag solution containing 1.5 % glucose combined with a nocturnal exchange with Extraneal.

The study consists of three study periods, with a total duration of 84 days. The potentially eligible patients entered a 4-week run-in period (screening period) to identify eligible subjects. Depending on the previous peritoneal dialysis prescription, during the screening period, patients were assigned to Group A or Group B, with Group A receiving standard solution with 2.5% glucose for the nocturnal exchange and Group B 1, 2 or 3 diurnal exchanges with 1.5% glucose solutions and one nocturnal exchange with icodextrin (Extraneal), continuing their previous PD prescription. Subjects enrolled entered the intervention period lasting 4 weeks. The subjects in Group A received a bag with the experimental solution (IXP15, equivalent in osmolarity to the glucose 2.5% solutions) for the nocturnal dwell, and subjects included in Group B received 1, 2 or 3 bags with the experimental solution (IXP07, equivalent in osmolarity to glucose 1.5% solutions) for the daily exchanges and a bag with icodextrin solution for the nocturnal dwell.

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For all subjects, the Investigator performed clinical and laboratory assessments to evaluate the potential changes in peritoneal membrane function consequently to the use of the experimental solution. Peritoneal dialysis performance tests during the investigational treatment period were compared with results during the follow up period with glucose.

During the 4 week follow-up period, subjects returned to the use of standard solution with 2.5% glucose for the nocturnal exchange (Group A) or of the solution with 1,5 % glucose for diurnal exchanges (Group B) and went to the Center on day 42 and 56 to undergo study visits. For each subject, the study procedures ended with completing the follow-up period (day 56).

NUMBER OF PATIENTS:

Planned: 80 patients. Analysed: 12 patients

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Inclusion criteria

1. Age ≥18 years;
2. Diagnosis of ESRD treated for at least three months with CAPD, as stated by the medical staff of the center;
3. Stable clinical condition within four weeks before screening period, certified by medical/surgical history, physical examination and laboratory exploration;
4. Hemoglobin level ≥9g/dL;
5. Absence of acute peritonitis and/or peritoneal catheter infection (either exit site or subcutaneous tunnel) episodes within three months before selection;
6. To understand and sign an informed consent form.

For patients who were included in Group B, the following criteria were fulfilled too:

7. Be treated with Extraneal (nocturnal exchange bag solution) for at least 1 month
8. Be treated with 1, 2 or 3 diurnal exchange bag solutions (solution bags with 1,5% glucose) and one nocturnal exchange bag solution with icodextrin (Extraneal).

Exclusion criteria

Patients who fulfilled any of the following criteria were not enrolled:

1. History of alcohol or drug abuse in the last six months before selection for the study;
2. Androgen therapy in the last six months before selection;
3. Active infections;
4. History of congestive heart failure stage III and IV NYHA;
5. History of major cardiovascular events like stroke, acute myocardial infarction, coronary or other arterial revascularization procedures in the last three months before selection;
6. Clinically relevant cardiac arrhythmia;
7. Clinically relevant abnormalities of functional hepatic tests;
8. Therapy with L-carnitine or its derivatives in the last three months before selection;

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9. Pregnancy, lactating women or female subjects of childbearing potential who do not use an effective method of contraception;
10. Presence of relevant chronic medical conditions that could suggest exclusion of patient from the study or could interfere with assessment of study parameters, especially if the life expectation is less than one year;
11. Participation in another clinical study within the past month;
12. Known allergic reactions to L-carnitine or xylitol.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER(s):

During the 4-week Intervention Period, all patients enrolled in the study received:

- GROUP A: product code IPX15, containing glucose (0.5%), Xylitol (1.5%) and L-Carnitine (0.02%)) used for the nocturnal exchange, for 28 days;
- GROUP B: product code IPX07, containing glucose (0.5%), Xylitol (0.7%) and L-Carnitine (0.02%)) used for the diurnal exchanges (1, 2 or 3 exchanges), while a bag with icodextrin solution was used for the nocturnal exchange, for 28 days.

Both drugs were administered for peritoneal dialysis.
Batches of product code IPX15: 1905
Batches of product code IPX07: 2100460 and 1902
The primary packaging was a single-chamber polypropylene bag containing the experimental solution. The solution bags were provided with a transfer set for peritoneal dialysis, with an empty polypropylene bag for collection of effluent for each peritoneal dialysis and a Luer-Lock connection to the patient. The system is consistent with Twin-Bag Baxter. Each bag with the transfer set was over-wrapped with formable film/envelopes before sterilisation.
IXP15 and IXP07 batches were manufactured and labelled according to GMP by Galenica Senese, Via Cassia Nord, 351, Monteroni d'Arbia (Siena) Italy. All study medications were labelled according to the EU Regulation (Eudralex Vol 4 Annex 13, Investigational Medicinal Products).
The bags were stored at temperatures between 4°C and 30°C, protected from light, in a secure, lockable place with limited access only for persons involved in the study.

DURATION OF TREATMENT:

The duration of treatment was 28 days

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER:

None

CRITERIA FOR EVALUATION:

Outcome variables for safety and tolerability assessment were:

- incidence and severity of adverse events during the intervention and follow-up periods;
- changes in the subjective questionnaire on the patient's perception of well being at days 28 and 56 as compared to baseline.
- occurrence of abnormal laboratory values at days 14, 28 and 56 as compared to baseline.
- change in CA 125 and protein levels in ultrafiltrate from baseline to day 28 and 56.

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The following efficacy parameters were assessed during the study:

- Peritoneal Equilibrium Test (PET);
- weekly total urea Kt/V (KT/V);
- weekly total creatinine clearance (CrCL);
- Peritoneal ultrafiltration (UF);

Free carnitine and its acyl-derivative in blood, urine and peritoneal effluent.

STATISTICAL METHODS:

Study Populations:
Study population consists of all subjects in the study database who completed treatment.
All patients who used at least one bag with the experimental solution or with the standard solution were included in the safety analysis.

Sample size:
The sample size has been calculated based on the following hypothesis about a subjective questionnaire on the patient's perception of wellbeing. The null hypothesis (H0) presupposes the state of health measured at the end of both treatments (experimental (day 28) and standard treatment (day 56)) remains unchanged. In contrast, the alternative hypothesis (H1) presupposes an improvement in the state of health at the end of the experimental treatment of at least one point within the 1 to 5 scale. Given $\Delta=1$, α, β equal to 0.05 and 0.20, respectively, with a standard deviation of the difference Δ equal to 1.5, at least 40 patients (20 Group A + 20 Group B) had to be enrolled so that 80 treatments (40 for Group) will be administered (each patient will be treated first with the experimental treatment and then with the standard treatment).

Primary Assessment:
Safety outcomes,

- incidence and severity of adverse events during the intervention and follow-up periods;
- changes in the subjective questionnaire on the patient's perception of wellbeing at days 28 and 56 as compared to baseline.
- occurrence of abnormal laboratory values at days 14, 28 and 56 as compared to baseline.
- change in CA 125 and protein levels in ultrafiltrate from baseline to day 28 and 56.

have been evaluated descriptively.

Secondary efficacy assessment;
The secondary objectives were to assess the performance of the peritoneal dialysis with the investigational product, specifically the peritoneal clearances and peritoneal transport characteristics with respect to Day 0 and the follow-up period, to ensure that the investigational product allows for effective peritoneal dialysis at least non-inferior of glucose solutions. The tests used in the study (Kt/v, PET, Creatinine clearance and Ultrafiltration) show the effects of the PD product on peritoneal dialysis performance,
Since the purpose of these analyses is purely exploratory and the number of patients involved is largely below the number foreseen in the study protocol, the analysis was conducted with a "non-parametric" approach, using the "Wilcoxon Matched-Pairs Signed-Ranks test" and without any correction of the "p-value" for multiple comparisons. As regards the comparison between the two treatment periods (Period 1: "Intervention Period" and Period 2: "Follow up Period"), the changes from Day 0-Day 28 and Day 28-Day 56 were compared, respectively.

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Adverse Events (AE)

AE, laboratory abnormalities, vital signs, ECG have been evaluated descriptively.

SUMMARY OF RESULTS AND CONCLUSIONS:

Enrollment:

Three centers screened 15 subjects and 13 were enrolled between October 2019 and December 2021. One subject was lost to follow-up and did not complete treatment (patient 01-010 in Group A discontinued before day 28 visit). Overall, 12 subjects received trial treatment: 6 (50%) the treatment Group A (receiving a bag with the experimental solution IPX15 for the nocturnal dwell) and 6 (50%) the treatment Group B (one or two bags with the experimental solution IPX07 for the daytime exchanges and a bag with icodextrin solution for the nocturnal dwell). All 12 subjects completed the treatment.

Baseline Demographics:

Study enrolled 9 male and 6 female patients, mean (±SD) age of 68.58±11.38 years (median 68.5 years, min-max 37-82 years). All patients were Caucasian, mean (±SD) weight was 79±14.67 kg (median 81 kg, min-max 51-100 kg), and mean (±SD) height 169±7.98 cm (median 169.5 cm, min-max 155-186 cm)

Efficacy Analyses:

In this study, due to the incomplete sample size enrolled (12 patients of the 40 planned), data from the two treatment groups (A and B) have been pooled to increase the informative value of the study. The primary study objectives were to evaluate the safety and tolerability of the experimental solutions. The secondary objectives were to assess the performance of the peritoneal dialysis with the investigational product, to ensure that the investigational product allows for an effective peritoneal dialysis, at least non-inferior of glucose solutions.

Weekly Total Urea (Kt/V)

There are no statistically significant differences for the changes in Kt/V between day 0 (end of run-in with glucose PDS) and day 28 (end of treatment with the investigational product) [$\Delta = 0.106 \pm 0.239$; P=0.164], between day 28 and day 56 (end of follow-up period with glucose PDS + icodextrin PDS nightly) [$\Delta = -0.049 \pm 0.219$; P=0.3613], and between day 0 and day 56 [$\Delta = 0.058 \pm 0.340$; P=0.7646], There is no statistically significant difference comparing the two treatment periods, the intervention period (day 0-day 28) and the follow-up period (day 28-day 56) [$\Delta = -0.156 \pm 0.325$; P=0.1162)].

Peritoneal Equilibration Test (PET)

Results show a statistically significant difference for the change in PET creatinine between day 0 (0.573 ± 0.130) and day 28 (0.643 ± 0.058), [$\Delta = 0.070 \pm 0.148$; **P = 0.0322**]. Comparing the two treatment periods, there is a decrease in the PET values in the follow-up period (day 28 - day 56) compared to the intervention period (day 0 - day 28), which is statistically significant [$\Delta = -0.102 \pm 0.170$; **P = 0.0225**]. There are no statistically significant differences for PET creatinine between day 28 and day 56 [$\Delta = -0.025 \pm 0.057$; P=0.2676] and between day 0 and day 56 [$\Delta = -0.051 \pm 0.157$; P=0.5156],

For PET glucose, there are no statistically significant differences between day 0 and day 28 [$\Delta = 0.037 \pm 0.103$; P=0.2695], between day 28 and day 56 [$\Delta = 0.013 \pm 0.69$; P=0.6563], day 0 - day 56 [$\Delta = 0.050 \pm 0.089$; P= 0.0547]

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Weekly Total Creatinine Clearance

There are no statistically significant differences between day 0 and day 28 [Δ=2.71 ± 12.09; P= 0.3394], between day 28 and day 56 [Δ= -4.25 ± 11.42; P= 0.5195], and day 0 - day 56 [Δ= -1.11 ± 13.17; P= 0.5771]. Comparing the two periods (the follow-up period and the intervention period), there is no statistically significant difference [Δ= -10.92 ± 22.75; P= 0.46].

Total Ultrafiltration

There is no statistically significant difference comparing day 0 and day 28 [Δ= 37.50 ± 128.14; P= 0.5000]. However, there is a statistically significant difference between day 28 (354.17 ± 264.11) and day 56 (483.33 ± 289.46) [Δ= 129.17±143.75; **P = 0.0117**], and between day 0 (316.67 ± 271.64) and day 56 (483.33 ± 289.46) [Δ= 167.67±154.23; **P=0.0039**). There is no statistically significant difference comparing the two treatment periods [Δ= 91.67 ± 224.45; P=0.24].

Serum, urinary, and dialysate L-Carnitine and Acetyl-L-Carnitine

Samples for free carnitine and its acyl-derivatives levels in blood, urine, and peritoneal effluent were obtained from all 12 patients. Table 2.1 shows concentrations of serum, urinary, and dialysate L-Carnitine and Acetyl-L-Carnitine (mean±SD). Figure 2.1 shows graphically the profile of the curves of serum L-carnitine values of each patient, over time. Figure 2.2 shows the serum L-carnitine levels per group (A and B) over time. Please note that patients of Group A received one solution bag of the investigational product (IXP15 containing carnitine 0.02%) during the nocturnal exchange. Patients of Group B received 2 solution bags (IXP07, containing L-carnitine 0.02%) during the diurnal exchanges, apart from the patient 01-002, who received only one bag (only one diurnal exchange).

Table 2.1. Mean (SD) serum, urinary and dialysate L-Carnitine and Acetyl-L-Carnitine

	Day 0	**Day 14**	**Day 28**	**Day 42**	**Day 56**
Serum L-carnitin	51,08±23.31	139.08±46.88	149.41±38.80	66.5±12.41	59±11
Serum Acetyl-L-carnitine	9.58±4.21	35.16±18.39	34.66±17.41	12±4.49	10.16±3.10
Urine L-carnitine	45.33±45.25	322.77±191.48	255.26±122.57	43.26±32.87	35.94±15.74
Urine Acetyl-L-carnitine	16.07±21.49	134.74±43,68	102.14±41.33	14.61±8.78	17.14±15.46
Dialysate L-carnitine	38.74±20.83	272.58±174.54	142.91±71.87	51.5±11.47	48.39±7.72
Dialysate Acetyl-L-carnitine	7.05±4.18	26.84±18.49	30.68±15.97	9.06±4.42	8.11±2.78

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Figure 2-1 Overlay of serum L-carnitine levels by patients

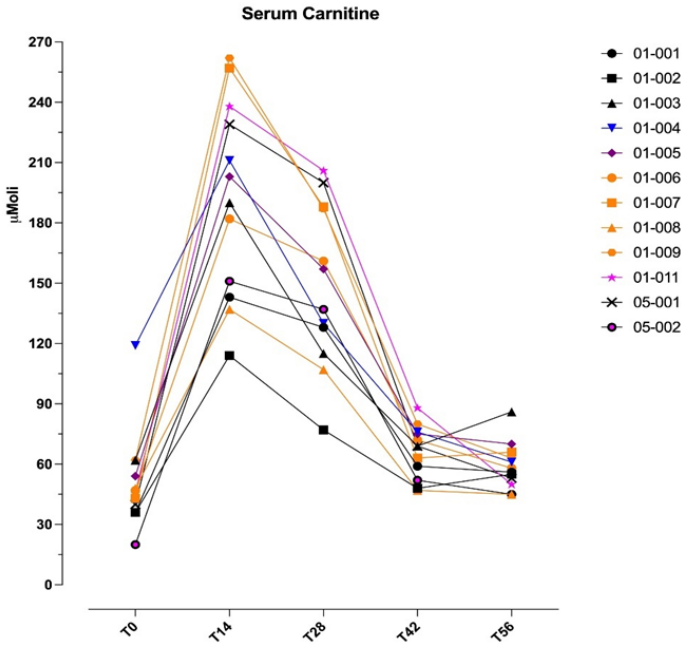
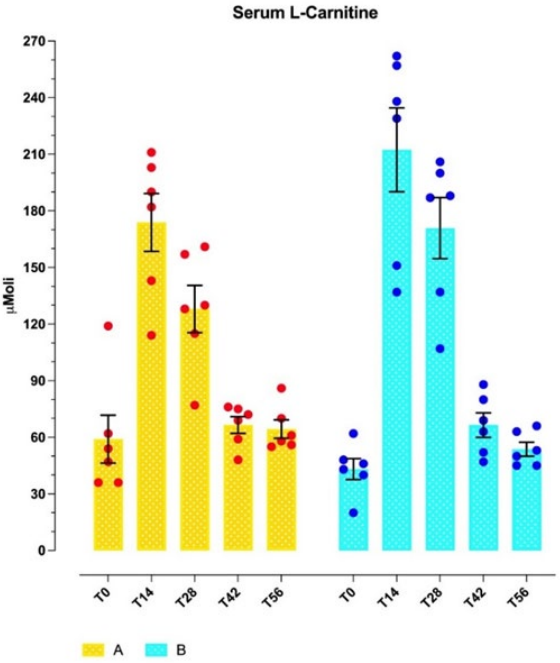


Figure 2.2 Serum L-carnitine by treatment group



Safety

A total of 13 patients received the investigational product. Seven patients (Group A) received 1 bag of IXP15 for nocturnal CAPD exchange, and 6 other patients received IXP07 for 1, 2, 3 diurnal exchanges (5 patients received 2 exchanges and 1 patient received 1 exchange). One patient (Subject 01-010 in Group A was lost to follow-up before the day 28 visit and received 14 bags of investigational product only).

During the study, there were 480 single administrations of investigational products (180 for IXP15 and 300 for IXP07)

Adverse Events:

Overall, 9 AE by 5 subjects (38.46%) were reported during the treatment phase. Only 1 AE was in a Group A patient (Subject 01-004, received IXP15 and had hyperphosphatemia which was mild in intensity and considered not related). No adverse event led to the discontinuation of the study medication, death, or was considered related to the investigational product, AEs is presented in Table 2.2.

Vital signs, clinical examinations, and electrocardiographic findings did not raise safety concerns. No patient showed serious signs of overhydration or had appreciable changes in body weight during the study.

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Table 2-2. Summary of Adverse Events.

Adverse Events	Number of AEs
Anemia	1
Turbid peritoneal fluid	1
Hyperphosphataemia	1
Macroglossia	1
Insomnia	1
Dispnea	1
Itching	1
Swollen legs	1
Mild bilateral legs edema	1

Laboratory results

All hematology, and biochemistry, including uric and lactic acid parameters were assessed as "Normal" or "Not Clinically Significant" between Day 0 and Day 56.

CA125 is a glycoprotein with high molecular weight considered as a marker of the mesothelial cells mass. In peritoneal dialysis patients, CA125 in dialysate is normal, but a high concentration in peritoneal effluent suggests a local release of mesothelial cells. A decrease of CA125 level in peritoneal effluent over time indicates the loss of mesothelial cells, thus CA125 being an in vivo marker of peritoneal solution biocompatibility.
Similarly, the loss of proteins in the ultrafiltrate (peritoneal effluent) will be used as a marker of the experimental solution tolerability. Results show that CA125 and proteins in the ultrafiltrate are quite stable between patients and do not reduce over time.

CONCLUSIONS

The study had a premature conclusion due to difficulties in enrolling patients. Data on 13 enrolled patients, with 12 completed the study, were available at the time of freezing of the database for the statistical analysis. There were 480 single administrations of the investigational product for peritoneal dialysis.

Tolerability was good. Overall, 9 AEs by five subjects (38.46%) were reported. A summary of Adverse Events is reported in Table 12.3 and Listing 16.11. No adverse event led to the discontinuation of the study medication, death, or was considered related to the investigational product. All AEs were mild or moderate in intensity. There were no Serious Adverse Events. Vital signs, clinical examinations, and electrocardiographic findings did not raise safety concerns. No patient showed severe signs of overhydration or had appreciable changes in body weight during the study. Haematology and biochemical parameters, including uric and lactic acids, showed no clinically significant changes at the different time points of the study. Oxalic acid levels did not change during the study.

CA125 is a glycoprotein with high molecular weight considered a marker of the mesothelial cell mass. In peritoneal dialysis patients, CA125 in the dialysate is normal, but a high concentration in peritoneal effluent suggests a local release of mesothelial cells. A decrease in CA125 level in peritoneal effluent over time indicates the loss of mesothelial cells. Thus, CA is an in vivo marker of peritoneal solution biocompatibility.

Similarly, the loss of proteins in the ultrafiltrate (peritoneal effluent) will be used as a marker of the experimental solution tolerability. Results show that CA125 and proteins in the ultrafiltrate are stable between patients and do not reduce over time.

Regarding efficacy, no statistically significant differences have been seen between the treatment period with the investigational product (days 0 to 28) and the follow up period with glucose (days 28 to 56) for weekly Kt/V and weekly Total Creatinine Clearance.

Evaluation of peritoneal membrane characteristics by Peritoneal Equilibration Test (PET) showed that patients were average transporters. Results show an increase in the PET creatinine from day 0 to day 28, which was statistically significant (P=0.0322 with Wilcoxon Matched-Pairs Signed-Rank test). A direct comparison between periods (changes in the treatment period compared with changes during the follow-up period) showed a decrease in PET creatinine during follow up, which was statistically significant (P= 0.0225). No statistically significant difference in PET glucose has been seen between day 0 and day 28, between day 28 and day 56, and day 0-day 56. Interestingly, while PET creatinine slightly increased during the treatment and decreased during follow-up, PET glucose remained stable over the study (increased without statistical significance). If these data will be confirmed, it might be speculated that the investigational medicinal product (IMP) improves the peritoneal clearance of small solutes (creatinine) without an increase in glucose absorption and a consequent osmolar gradient dissipation, as expected by the Twardowsky graph (92).

For Total Ultrafiltration, a statistically significant difference has been seen comparing day 28 (end of the treatment period with the IMP) and day 56 (P= 0.0117). Also, the difference between day 56 and day 0 was statistically significant (P= 0.0039). However, a comparison between periods (changes during the follow-up period compared with changes in the treatment period) was not significant. Ultrafiltration showed a positive trend during the study, suggesting a potential carry-over effect. Considering the intrinsic variability of ultrafiltration data, this study is clearly insufficient to draw any conclusion and further investigations are needed.

The determination of L-carnitine in serum shows profiles between days 0, 14, 28, 42, and 56, representing an increase of concentration during the treatment period (day 0 to 28), which reduced up to day 42, returning to values similar to the baseline by day 56. Urine and dialysate concentrations correspond to the changes seen in the blood.

Six patients in group A (receiving a bag with the experimental solution IPX15 for the nocturnal dwell) and six patients in group B (one or two bags with the experimental solution IPX07 for the daytime exchanges and a bag with icodextrin solution for the nocturnal dwell) completed study treatments. Due to the incomplete sample size enrolled (12 patients of the 80 planned), data from the two treatment groups (A and B) have been pooled to increase the informative value of the study. The two treatment groups have been merged for statistical analysis.

The primary study objectives were to evaluate the safety and tolerability of the experimental solutions. The secondary objectives were to assess the performance of the peritoneal dialysis with the investigational product, specifically the peritoneal clearances and peritoneal transport characteristics from day 0 to day 28 and the follow-up period, to evaluate if the investigational product allows for adequate peritoneal dialysis, at least non-inferior of glucose solutions. The test methods used in the study (Kt/v, PET, Creatinine clearance, and Ultrafiltration) show the effects of the PD product on peritoneal dialysis.

Taken together, safety and efficacy data suggest the investigational product is well tolerated and should be as effective as commercially available glucose-based PD solution. A confirmatory study is needed to demonstrate its non-inferiority compared with commercial glucose-based PD solutions.

DATE OF REPORT: 24 January 2024

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AC	Acetyl-Carnitine
CAPD	Continuous Ambulatory Peritoneal Dialysis
CAT	Carnitine Acetyl-Transferase
CoA	Coenzyme A
CRF	Case Report Form
$D/P_{creatinine}$	Creatinine-based peritoneal equilibration test. Dialysate concentration (D) over plasma (P)
$D/D_{0\ glucose}$	Glucose-based peritoneal equilibration test. Dialisate concentration at time t (D) over dialysate concentration at infusion (D_0)
ECG	Electrocardiogram
ESRD	End Stage Renal Disease
FC	Free Carnitine
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HD	Hemodialysis
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
i.v.	intravenous
LC	L-Carnitine
CNS	Central Nervous System
Os	orally
PET	Peritoneal Equilibration Test
PD	Peritoneal Dialysis
PDH	Pyruvate Dehydrogenase
QA	Quality Assurance
RBC	Red Blood Cells
SAE	Serious Adverse Event
TC	Total Carnitine
TMF	Trial Master File
WBC	White Blood Cells

5 ETHICS

5.1 Independent Ethics Committee or Institutional Review Board

The protocol for this study and any accompanying material provided to subject (such as subject information sheet and consent form) were submitted to independent Ethics Committees (EC). Approval from all the EC and, where required, from Health Authorities, have been obtained before starting the study. Any modifications made to the protocol after receipt of the EC approval were submitted by the Investigator to the ethical committee according to the local procedures and regulatory requirements. These EC operated according to the local Laws and ICH Guidance. The list of EC is provided in Appendix 16.1.3. Details on the procedures of authorization are provided below. The study was approved by:

- the Ethics Committee of University G. d'Annunzio of Chieti-Pescara (project identification code IP-001-09) on 23/09/2010 Protocol Version V3; Protocol Amendment 1 (Protocol Version 4) was approved on 7/7/2011, Amendment 2 on 22/11/2018 (Protocol V5), Amendment 3 on 10/9/2020 (Protocol V6).
- the Ethics Committee of Bari Policlinico Hospital on 1/2/2012 (Protocol V3); Amendment 2 was approved on 19/2/2020 (Protocol V5), and Amendment 3 on 9/9/2020 (Protocol V6).
- and the Ethics Committee of Rome Policlinico Gemelli on 10/11/2020 (Protocol V6).

5.2 Ethical Conduct of the Study

The Investigator ensured that this study was conducted in full conformance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, South Africa, and Edinburgh) or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study fully adhered to the principles outlined in Guideline for Good Clinical Practice (GCP), International Conference on Harmonisation (ICH) Tripartite Guideline (ICH GCP E6), or with local law if it afforded greater protection to the subject.

This Clinical trial has been carried out outside the European Union and meet the ethical requirements of Directive 2001/20/EC, in conformity with Art.8(ib) of Directive 2001/83/EC.

5.3 Patient Information and Consent

It was the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For subjects not qualified or incapable of giving legal consent, written consent must have been obtained from the legally acceptable representative (if permitted by local regulations). If new safety information resulted in significant changes in the risk/benefit assessment, the consent form was to have been reviewed and updated if necessary. All subjects (including those already being treated) were to be informed of the new information, given a copy of the revised form and required to give their consent to continue in the study. A sample of the patient informed consent is provided in Appendix 16.1.3.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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This study was conducted at three (3) sites in Italy. A list of investigators is presented in Appendix 16.1.4.

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7 INTRODUCTION

The uremia (kidney failure) describes a state characterized by the accumulation of uremic toxins leading to multiple organ damage. Renal replacement therapy (dialysis or kidney transplantation) is the recommended treatment modality for patients with advanced chronic renal failure. These patients are known as End-Stage Renal Disease (ESRD) patients.

In current clinical practice, Peritoneal Dialysis (PD) is the preferred method for patients still preserving renal function.

Peritoneal dialysis is based on the solute and fluid exchange between the peritoneal capillary blood and the dialysis solution across the peritoneal membrane. During peritoneal dialysis, a quantity of solution – named PD solution or PD dialysate – is infused into the peritoneum through a catheter. Continuous Ambulatory Peritoneal Dialysis (CAPD) is a particular technique of peritoneal dialysis consisting in three to five daily exchanges of 0.5 to 3L each, done by the patient itself. During the exchange, the dialysis bag is connected to the peritoneal catheter and the PD solution (usually 2L) is instilled by gravity in 10-20 minutes. Then, the patient can move freely and continues his normal activities. After a dwell period of several hours (usually 4-6 hours), the dialysate is evacuated from the peritoneal cavity via the catheter, also by gravity, and a new quantity of PD solution is instilled instead. In CAPD, the dialysis occurs continuously, 24-hours around.

CAPD is recommended especially in elderly and cardiovascular patients because it assures a stable cardiovascular status, a better control of arterial high blood pressure and steady biochemical parameters. As recently demonstrated, CAPD allows longer preservation of the renal residual function as compared to hemodialysis.

According to its composition, the PD solution can remove or infuse solutes from or to the patient. The solutes are transported across the peritoneal membrane by convection (movement of solutes related to fluid removal) or by diffusion (according to the concentration gradient of the solute between blood and dialysate). Since convection is the main mechanism and fluid removal (ultrafiltration) requires a higher osmolality of the dialysate in relation to serum, all PD solutions contain an osmotic agent.

Many osmotic agents were proposed, but the most used low-molecular weight osmotic agent is glucose. However, the peritoneal membrane is not impermeable to glucose, so that a rapid reduction of the osmotic gradient and an increase of serum carbohydrates are seen in CAPD patients. Almost 50-60% of the instilled glucose into peritoneal cavity is absorbed during a usual dwell time (4-6 hours). About 100-300g/day of glucose are absorbed when the used glucose concentration in PD solutions is 1.5%-4.5% (1-6).

Glucose has long-term detrimental effects on the peritoneum, which ultimately may result in ultrafiltration failure of the peritoneal membrane. Furthermore, absorption of the glucose from dialysate enhances the disturbances of carbohydrates metabolism, which is already impaired in uremic state. Advanced chronic renal failure is associated with insulin resistance and disorders of glucose, lipids and amino acids homeostasis. (7-9)

Compared to hemodialysis, in CAPD patients a higher *à jeun* level of serum insulin, an augmented response to insulin at every dialytic exchange and an elevated 24-hour profile of insulin are found. (2) A high level of hyperglycemia is observed in patients treated with higher doses of glucose, but a slight hyperglycemia and hyperinsulinemia occur in all CAPD patients. (10)

In CAPD patients were reported more frequent diabetes mellitus and hyperlipidemia (especially hypertriglyceridemia and abnormalities of serum lipoproteins), partially accounted for by the glucose absorption. (3, 4, 5, 11-16). Although in the general population with healthy kidney function an altered lipoprotein profile is believed to increase the risk of cardiovascular disease, in dialysis patients (HD and PD) this is much less evident. Actually, it has clearly been shown that (a) an inverse relationship between survival and hyperlipidemia (high LDL-cholesterol or triglycerides) there exist in dialysis patients, and that (b) statin treatment does not offer any survival benefit in both diabetic and non-diabetic dialysis patients with altered lipid profile (17-19).

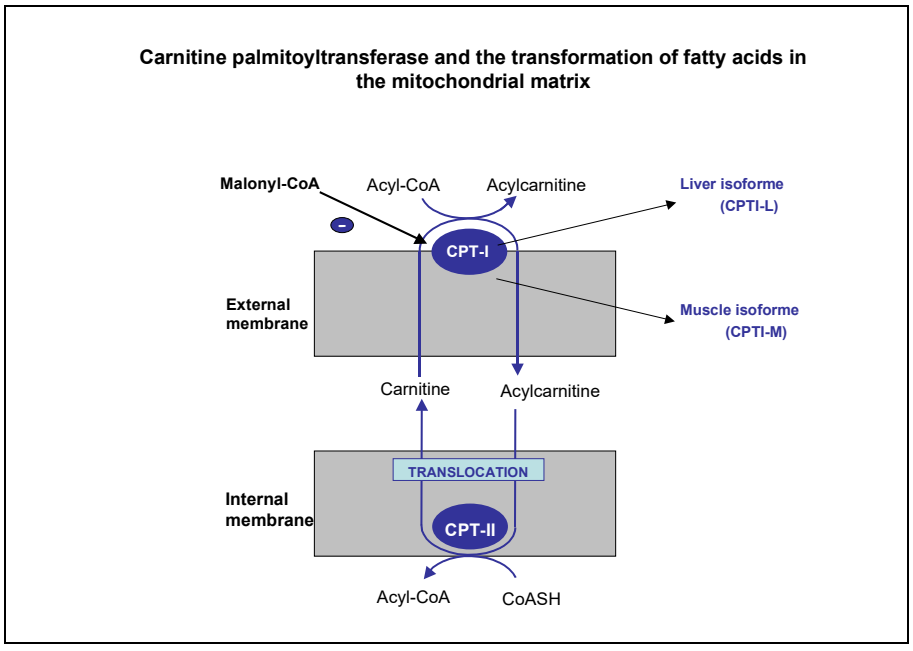
Pharmacology

Biological, pharmaco-metabolic and safety properties of L-Carnitine

Biological properties

L-Carnitine (LC) is a naturally occurring substance involved in the translocation of long-chain fatty acids across the mitochondrial membrane. The roles of carnitine in regulation of the fatty acids oxidation, ketogenesis and production of cellular energy are well known. (20-24).

Figure 7.1. The involvement of carnitine in fatty acids transformation in the mitochondrial matrix



Cytosolic long-chain fatty acids, which are present as CoA esters, are trans-esterified to L-carnitine in a reaction catalysed by carnitine palmitoyltransferase I (CPT I) at the mitochondrial outer membrane (**Figure 7.1**). In this reaction, the acyl moiety of the long-chain fatty acids is transferred from CoA to the hydroxyl group of carnitine. The resulting long-chain acylcarnitine esters are transported over the inner mitochondrial membrane via a specific carrier, carnitine-acylcarnitine translocase (CACT). At the matrix side of the mitochondrial membrane, the long-chain fatty acids are transesterified to intramitochondrial CoA, a reaction catalysed by carnitine palmitoyltransferase II (CPT II). The released carnitine can then leave the mitochondrion via CACT for another round of transport. In the mitochondrial matrix, the enzyme carnitine acetyltransferase (CAT) is able to reconvert short- and medium-chain acyl-CoAs into acylcarnitines using intramitochondrial carnitine. These acylcarnitines can then leave the mitochondria via CACT. In addition, LC is able to modulate the intra-mitochondrial pool of free acetyl-CoA and CoA, through the action of carnitine acyl-transferase (CAT). Elevated acetyl-CoA levels in mitochondria are known to inhibit enzymes involved in glucose metabolism such as pyruvate dehydrogenase (PDH).

Pharmaco-metabolic properties

A large body of experimental evidence indicates that LC exerts *in vitro* and *in vivo* pharmacological actions at concentrations significantly higher (low millimolar range) than those physiologically present in the extra- and intra-cellular milieu (low micromolar to low millimolar range) [see also 24].

Given the very poor pharmacokinetic properties of LC (very low bioavailability, very efficient kidney excretion, etc), the achievement of a LC plasma and target organ exposure to elicit the expected pharmacological response should be feasible in PD patients rather than in patients with a normal kidney function. Indeed, it is well known that intravenous LC supplementation to HD patients results in more than fivefold increase of LC plasma concentration (i.e., 20 mg/kg given at the end of each dialytic session for 12 weeks), whereas a comparable dosage of LC, orally supplemented to subjects with a healthy kidney, modestly increases plasma LC levels (25). It should also be noted that PD patients, as well as HD patients, have lower free LC plasma levels, LC deficiency, along with an altered ratio of free vs acyl-carnitines, LC insufficiency (26-28). Thus, in addition to potential pharmacological actions (see also below), LC administration would also correct LC deficiency in PD patients.

The work published by Ferranini et al. is probably the most convincing and detailed evidence on the action of LC on glucose consumption in healthy human volunteers (29). During a short term euglycemic hyperinsulinemic clamp, intravenous LC infusion was administered to achieve a steady four-fold increase in basal serum LC levels.

Exogenous LC infusion was associated with a statistically significant increase of whole body glucose utilization and this effect was more pronounced in the subjects with higher rates of glucose disposal. Since net rates of insulin-induced glucose oxidation were similar with or without LC, the LC-induced enhancement of total glucose metabolism was quantitatively accounted for by a 50% increase in non-oxidative glucose disposal. In addition, plasma acety-L-carnitine levels significantly increased during LC infusion, suggesting that the administration of exogenous LC was able to affect the intra-mitochondrial pool of acetyl-CoA.. Using a similar experimental protocol and clamp technique

Mingrone et al have later reported that even in diabetic subjects the intravenous LC infusion increases glucose consumption (30). These studies unambiguously demonstrated that LC stimulates muscle glucose consumption by relieving acetyl-CoA inhibition of PDH. Indeed, in skeletal muscle of diabetic and/or insulin resistant subjects, insulin appears to be unable to mediate the switch from lipid to carbohydrate oxidation, a state described as "metabolic inflexibility" [24]. The fasting diabetic/insulin resistant muscle is characterized by a blunted suppression of glucose oxidation and lower than normal rate of fatty acid oxidation, and in the fed state insulin is less able to stimulate muscle glucose oxidation. One of the components of the pathogenetic mechanism responsible for the impaired muscle glucose disposal observed in diabetic/insulin resistant patients may be associated with PDK activation by an increased size pool of intramitochondrial acetyl-CoA which would act synergistically with the increased expression of specific isoforms of PDHK, e.g. PDHK4 [31].

In ESRD patients, Gonal et al have shown that a single i.v. administration of LC improves insulin sensitivity as evaluated by an insulin tolerance test [32]. Biolo et al. in a randomized, matched-paired, double-blind, placebo controlled experimental design determined the capability of chronic intravenous LC supplementation in modifying insulin resistance and protein catabolism in non-diabetic HD patients [33]. LC treatment led to a statistical significant reduction of leucine oxidation rates and appearance from proteolysis during the clamp studies compared to the placebo group. Insulin-mediated glucose disappearance was significantly improved by LC only in those patients with greater baseline insulin resistance, selected according to the median value of insulin sensitivity before treatment. A more recent study has addressed the effects of 24-week oral acetyl-L-carnitine (1 g twice daily) therapy, an LC prodrug, on the glucose disposal rate (GDR), assessed by hyperinsulinemic euglycemic clamps, and components of the metabolic syndrome in nondiabetic subjects at increased cardiovascular risk a priori segregated into 2 groups with high GDR values (insulin-sensitive) and low GDR values (insulin-resistant), respectively [34]. Acetyl-L-carnitine treatment significantly increased GDR and improved glucose tolerance in patients with low GDR values (insulin-resistant), whereas it had no effects in those with higher GDRs.

Although the clinical studies described above did not attempt to evaluate the potential action of L-carnitine on hepatic glucose production in the diabetic condition, some clues may be found in a number of preclinical studies conducted on diabetic experimental models. In a study originally designed to evaluate the beneficial action of L-carnitine on diabetic heart [35], streptozotocin-treated diabetic rats were dosed for 6 weeks with a very high daily intraperitoneally dose of LC (3g/Kg); at the end of the treatment, the L-carnitine group showed a remarkable reduction of plasma glucose compared to diabetic control group. Importantly, the lowering of plasma glucose was associated with the reversal of both glucosuria and polydipsia. L-Carnitine treatment of non-diabetic rats did not affect plasma glucose levels [35]. Taking into account that L-carnitine treatment did not affect the hypoinsulinemic state of streptozotocin diabetic rats, and that in this diabetic model the severe hyperglycaemic state is mainly driven by an increased hepatic glucose production, it is possible that L-carnitine could have been acting, at least partly, through the inhibition of gluconeogenesis. Further evidence of the anti-gluconeogenic action of pharmacological doses of L-carnitine has recently been provided by Rajasekar & Anuradha [36].

In this study, Wistar rats were fed for 1 month with fructose as the sole source of carbohydrate, an experimental model characterized by a severe impairment of insulin sensitivity, glucose intolerance, dyslipidemia and increased hepatic glucose production. Intraperitoneal L-carnitine administration (300 mg/kg/24h) for the entire period of fructose feeding normalized the elevated plasma glucose and insulin levels, and liver TG and FFA content in fructose fed rats [36]. These authors suggested that the ability of L-carnitine treatment to mitigate the adverse effects of the fructose diet was mainly due to the correction of L-carnitine deficiency induced as a result of the fructose load. If their interpretation is correct, it is possible that L-carnitine depletion in the liver could have affected FFA oxidation and, hence, the metabolic partitioning of long-chain fatty acyl-CoA towards esterification, leading to steatosis and increased hepatic VLDL-triglyceride secretion. Amelioration of insulin-stimulated glucose disposal in an obese diabetic transgenic mouse model was obtained after a 3 week period of dietary L-carnitine supplementation (1g/kg/day) [37]. Withdrawal of L-carnitine treatment for 6 weeks re-established the original diabetic state, though a further week of L-carnitine treatment reversed the loss of insulin sensitivity. After this second treatment period with L-carnitine, fasting glucose levels were strongly reduced, implying that L–carnitine therapy could have improved hepatic insulin sensitivity and, hence, the insulin-suppressive action on hepatic glucose production in this diabetic mouse model [37]. In addition, it may be worth noting two recent clinical papers reporting on the efficacy of LC treatment in lowering Lp(a) in hypercholesterolemic (38) and newly diagnosed diabetic patients (39).

Taken together, these observations suggest that LC administration at pharmacologic levels could be beneficial in improving the altered glucose and lipid homeostasis in PD patients.

Safety properties

The toxic effects of the intraperitoneal administration of LC were investigated in mice and rats. The DL50 is 12g/kg in mice and 8g/kg in rats, respectively (study performed in 1982 - first introduction of the GLP). With doses of 6.3g/kg in mice and 7g/kg in rats, no adverse events were observed in all the animals. More recent, another two studies regarding the peritoneal and systemic tolerability were performed on Sprangue Dawley rats. The first one consisted in a single intraperitoneal dose of LC in 2mL standard solution of glucose. Three different concentrations were tested: 0.75%, 7.5% and 15% corresponding to doses of 15, 150 and 300mg/kg, respectively. The second study investigated rats treated for 7 consecutive days with intraperitoneal administration of LC in a standard solution of glucose, in different concentrations (0.75%, 7.5% and 15%) corresponding to doses of 15, 150 and 300mg/kg, respectively.

Finally, in order to evaluate the local tolerability, a third experiment was conducted in rabbits, which received a single subcutaneous dose of LC diluted with 1mL standard solution of glucose, using the same different concentrations (0.75%, 7.5% and 15% corresponding to doses of 15, 150 and 300mg/kg, respectively). These studies on toxicity and tolerability indicated that LC is well tolerated even in high doses.

Two different clinical studies were performed in CAPD patients by adding LC in the PD solution. Bazzato et al. demonstrated that a dose of 2g of LC, added to PD dialysate and administered during the nocturnal exchange, was well tolerated, restoring the level of LC and augmenting the lipid pattern in 6 from 7 treated patients. (40) Kopple, in a clinical trial on 5 CAPD patients who received 20mg/kg LC in PD solution at 8 a.m. for a period of 14 days, showed an improvement of nitrogen balance after the administration of LC and, also, a good tolerability (41).

Other two studies assessed the effects of L-Carnitine in haemodialysis (HD) patients. During the first study, LC was intravenously infused in a dose of 2g at the end of every haemodialysis session, three times weekly for 12 months (42), while in the second study a dose of 40mg/kg LC was infused at the end of every HD session, three times weekly for 6 months (43). The serum concentrations of total and free carnitine reached were 1297±256μmol/L and 756±336μmol/L in the first study, and 790±229μmol/L and 455±162μmol/L in the second study, respectively. Since in both studies no adverse events were found, we can conclude that LC is well tolerated even when very high plasmatic levels are obtained (100 times higher than physiological concentrations).

In a recent study on 4 CAPD patients, Bonomini et al. added LC in the PD solution bag for the nocturnal exchange (44). The patient's dialytic schedule consisted of 4 daily exchanges: 3 during the day and 1 during the night with PD solution containing 2.27% glucose. The osmotic properties between the 2.27% glucose solution bag used for nocturnal exchange and the 1.36% glucose solution bag supplemented with 5 grams (0.25 % w/v) of LC were compared. Parameters of dialysis efficacy (Kt/V, peritoneal equilibration test, creatinine clearance), ultrafiltration, diuresis, and body weight were assessed during the observation period (7 days before the first supplementation with LC) and the therapeutic period (5 consecutive days with nocturnal exchange performed with 5 grams of LC added to a 1.36% glucose solution bag). Also, the carnitine concentration in plasma, urine and peritoneal effluent from all the exchanges were determined. The daily ultrafiltration volume was stable, without significant individual variations. The study provided interesting results: the diuresis was preserved without significant variations, and the ultrafiltration (UF) obtained during the exchange with PD solution supplemented with LC was comparable with that resulting from the exchange performed with 2.27% glucose solution (showing even an improvement trend). Such similar results concerning UF were confirmed by the lack of variation in patients' body weight. The tendency of augmented ultrafiltration capacity of the bag supplemented with LC varied from 5% to 13%. As expected, the carnitine plasma level at the end of the study was increased within a tolerable pharmacological range and the steady state was reached in the fourth day of treatment. After reaching the stable level, the plasma concentration of free carnitine was around 1.2mM. From the total dose of carnitine administered during the five days of treatment, over 75% was removed through the main elimination routes. It should also be noted that LC concentration that will be used in the current proposed clinical trial will be 12.5-fold less (0.02%. w/v) than the one used in the above described clinical trial (0.25%, w/v).

Two additional clinical trials with PD solutions containing LC are in progress in diabetic and non-diabetic patients with ESRD in CAPD (ClinicalTrials.gov Identifier No NCT00755404 and NCT00755456, respectively)

No adverse reactions were noticed in all the above clinical trials mentioned suggesting a good tolerability of LC administration.

Biological, pharmaco-metabolic and safety properties of Xylitol

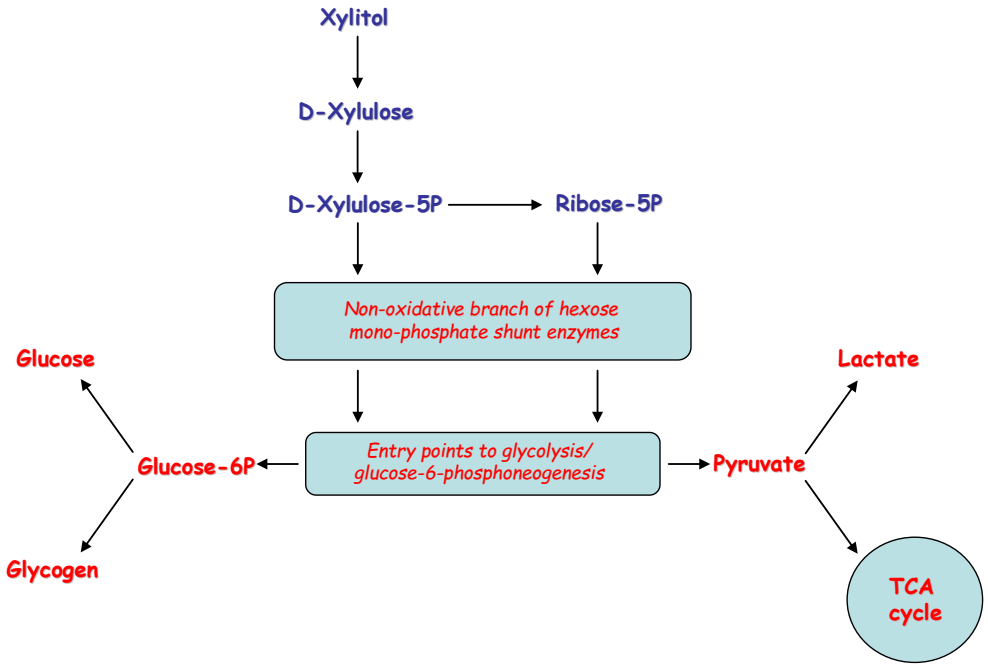
Biological properties

Xylitol is a five-carbon sugar alcohol, pentitol, which is manufactured by the reduction of D-xylulose. Xylitol is widely distributed in the plant and animal kingdoms. It is present in most wines as a fermentation product and in significant quantities in plums, strawberries, cauliflower, raspberries, etc. (45). In plums, approximately 1% of the dry weight is xylitol.

In mammals, the metabolism of xylitol varies according to the origin and of route of administration. Approximately 5-15 g of xylitol are formed per day in the human body, based upon the observation hat similar amounts of L-xylulose are excreted daily in urine in patients with essential pentosuria (46). Xylitol fed orally, depending on dosage, may not be totally absorbed. However, adaptation appears to occur in humans. This adaptation is most likely due to the transition of intestinal flora contents rather than to other biochemical mechanisms (47). Unlike glucose, xylitol is most likely absorbed by intestinal mucosa through passive or facilitated diffusion. Therefore, the rate of xylitol absorption is far slower than that of glucose. Liver is the major site for removal of either oral or intravenous xylitol. The liver appears to be responsible for 50-80% of xylitol metabolism in normal conditions. Some 15-20% of the remaining amount of parenterally administered xylitol can be used extrahepatically in the kidney, lung, erythrocyte, fat stores, and myocardium (46). The distribution of xylitol in eviscerated rats was found to be insulin independent. The removal of xylitol from blood appeared to be first-order kinetic process with a half-life of 19-23 minutes for non-adapted human adults, whereas its excretion is by simple glomerular filtration, and there is no readsorptive mechanism for it (46).

Xylitol is first oxidized to D-xylulose by the NAD-xylitol dehydrogenase, causing the NADH/NAD ratio to increase (see scheme below). The next step is the phosphorylation of D-xylulose to D-xylulose-5-phosphate by D-xylulose-kinase. D-xylulose-5-phosphate is an intermediate of the pentose phosphate shunt and it is metabolized to fructose-6-phosphate and glyceraldehyde phosphate by this pathway. Three molecules xylitol yield two molecules of fructose-6-phosphate and one molecule of glyceraldehyde phosphate. Fructose-6-phosphate can readily be converted to glucose and glycogen; glyceraldehyde phosphate either to glucose, glycogen or lactate. Most of the xylitol is rapidly converted to glucose and glycogen, and only small quantities are converted to lactate (**Figure 7.2**).

Figure 7.2. The metabolic fate of Xylitol



Pharmaco-metabolic properties

Parenteral nutrition is used clinically to optimize fluid, energy, nitrogen, electrolyte, and vitamin balance, especially in patients in shock, in a coma, with trauma, undergoing major surgery, or having burns, sepsis, diabetes, cancer cachexia, or acquired immunodeficiency syndrome (AIDS). These conditions are often characterized by suppressed insulin secretion or by hyperinsulinemia and insulin resistance, with consequent impaired glucose utilization (48). Indeed, infusions of glucose as an energy source in these conditions often require careful monitoring of blood glucose and the concomitant administration of insulin. Xylitol has been recommended as a parenteral nutrient because its entry into cells is insulin-independent, it is efficiently utilized after its intravenous infusion (without serious hyperglycemia), it stimulates less insulin secretion than does glucose, and it is less of an irritant to veins than is glucose when given in hyperosmolar solution (49).

Since 1970, it has been used in diabetics and for parenteral nutrition as a glucose substitute. It is also largely used at oral level in order to prevent the dental cavities since is able to form a complex with calcium stabilizing the salivary calcium-phosphate system. Xylitol has also been used as an osmotic agent in peritoneal dialysis showing some advantages over glucose: a better control of glycemia, enhancement of the endogenous insulin secretion and reduction of the administered insulin dose (50).

Xylitol has been used in Germany as a sugar substitute of glucose in total parenteral nutrition (see Totufusin OPX and ELKO-Mix, Baxter; Aminomix 4, Fresenius Kabi; Nutriflex Combi, BBraun) and the Ministry of Health authorized a maximal dose of xylitol of 3g/kg/day. These xylitol-based infusional products contain either xylitol alone or in combination with various nutrients (aminoacids, sugars, etc.).

Buoncristiani et al. assessed the use of xylitol as partial substitute of glucose in peritoneal dialysis bags (51). The observed benefits of these two sugars association were a lower 24-hours glycemic curve and a reduced response of insulin. Also, the lipid metabolism seemed to be improved and an increase of serum protein and albumin was found. Two patients who have used xylitol in PD solution were treated by peritoneal dialysis for 10 years and the only problem they experienced was a slight increase in serum uric acid levels.

Recently, Buoncristiani et al. investigated in vitro the biocompatibility and toxicity of a solution containing xylitol in different concentrations compared to glucose (52). The following effects were described:

1. Increase of the rabbit's mesothelial cells in the presence of solutions with low-glucose content or in complete absence of glucose.
2. In a single layer of mesothelial cells, the greater toxicity resulted from solutions without xylitol. Indeed, IL-1, expressed as a result of cellular injury, was increased in cells with higher levels of glucose. Conversely, PGI_2, expression of minor lesions, decreased with lower glucose concentration.
3. At the level of mesothelial cells, the concentrations of phospholipids and phosphatidil-choline, indispensable surfactants for normal functioning peritoneum, were higher in presence of xylitol.
4. The minor formation of giant cells suggested a scarce toxicity and a good biocompatibility of solutions without glucose.

The scarce toxicity and good biocompatibility of xylitol were demonstrated in various clinical trials that used parenteral administered xylitol.

A clinical trial conducted by Bazzato et al. investigated xylitol as an osmotic agent replacing glucose in end-stage renal disease insulin-dependent diabetics on CAPD (50). The therapeutic schedule, followed for a median duration of 8.7 months (range 5-11 months), consisted in 4 daily exchanges of 2L PD solution, from which 3 were with normal osmolality solution (Xylitol 1.5g/dL) and one with hyperosmolar solution (3g/dL). The total daily dose of xylitol administered via peritoneum with this protocol was 150g. The plasma xylitol level was 30mg/dL during the daily dwells and reached 80mg/dL during the nocturnal dwell. These concentrations had no influence on plasma osmolality.

In treated patients, it was noticed a significant improvement of lipid profile: triglycerides and cholesterol levels decreased after the first two months of treatment, while HDL-cholesterol increased, restoring the normal levels after 2-5 months. All these parameters remained until the end of the study. The elevated plasma levels of inorganic phosphorus observed during CAPD with glucose were significantly reduced 5 months after the commencement of the CAPD with xylitol.

The required exogenous insulin was reduced to half as compared to the amount administered during CAPD with glucose. The level of glycosylated haemoglobin was significantly lower during treatment with xylitol as compared to the therapeutic period with glucose, indicating a better control of diabetes mellitus.

During the observation period, a progressive increase of serum uric acid concentration was seen, requiring administration of allopurinol that induced a slow reduction of these values.

Lactic acid was enhanced during the entire treatment period, remaining however within normal range.

The dosage of 150g/day xylitol was well tolerated, without evidences of adverse effects or clinical signs of calcium oxalate deposition (50). Only when the xylitol dosage exceeded 150g/day, in patients who needed PD solutions with higher content of xylitol in order to augment the ultrafiltration effect, adverse events like nausea, vomiting or increased levels of serum bilirubin and transaminases occurred.

It should be mentioned that in our study the patients would be exposed to a maximum xylitol dosage of 36g/day, a value lesser than that used by Buoncristiani (55 g/day) and much less than that used by Bazzato (150 g/day) (50-52).

Safety properties

In 1986, the Federation of American Societies for Experimental Biology (FASEB) was commissioned by the U.S. Food and Drug Administration (FDA) to review all relevant data concerning xylitol and other polyols (www.cfsan.fda.gov/~lrd/fr960823.html). The FASEB report's scientific conclusions indicate that the use of xylitol in humans is safe. The report also affirms xylitol's acceptability as an approved food additive for use in foods for special dietary uses.

In 1996, the Joint Expert Committee on Food Additives (JECFA), a prestigious scientific advisory body to the World Health Organization and the Food and Agricultural Organization of the United Nations, confirmed that adverse findings in animal studies conducted in the 1970s are "not relevant to the toxicological evaluation of these substances (e.g., xylitol) in humans." JECFA has allocated Acceptable Daily Intake (ADI) of "not specified" for xylitol. ADI, expressed in terms of body weight, is the amount of a food additive that can be taken daily in the diet over a lifetime without risk.

An ADI of "not specified" is the safest category in which JECFA can place a food additive. The Scientific Committee for Food of the European Union (EU) also determined xylitol "acceptable" for dietary uses.

However, since it has been reported in the literature that xylitol infusion may increase lactate, urate and oxalate levels, which in turn may have potential side-effects, a thorough reappraisal of this issue in relationship to the use of xylitol in PD is reported below.

ULactate: In the Bazzato's paper, where the daily dose of xylitol administered intraperitoneally was 150 grams, serum lactate levels after 11 months of xylitol treatment were 17.5 mg/dL compared to 12.6 mg/dL before xylitol treatment (50). Since the normal plasma range of lactic acid is 6.7-21.6 mg/dL (Scientific tables Geigy), the modest increase observed remains within normal range. In the Buoncristiani experience, where the daily dose of xylitol administered intraperitoneally was 55 grams (almost 3 fold less than Bazzato), serum lactate levels after years of xylitol treatment were comparable to PD patients treated with glucose as an osmotic agent (52). Since we are planning to use lower (long exchange) or similar (short exchange) amounts of xylitol compared to that used by Buoncristiani, potential elevation of lactic acid in plasma is not an issue. It should be taken into account that even glucose infusion (i.v. or i.p.) may lead to increased plasma levels of lactic acid, which, under certain circumstances (thiamine deficiency), it may reach extremely high levels, leading to metabolic acidosis (53). In the PubMed there are several cases of severe lactic acidosis in thiamine deficient patients exposed to glucose given as a parenteral infusion.

Thus, even in the classic PD solution containing only glucose, it would not be a bad idea to either include in the bag or to treat PD patient with some thiamine, in order to improve acid-base homeostasis in PD patients. In principle, PD patients are prone to develop mild thiamine deficiency.

Urate: Elevated serum uric acid has been suggested as a feature of hyperinsulinemia and insulin resistance (54). Although a number of studies have further evaluated increased serum uric acid as a component of the Metabolic Syndrome, there is currently no satisfactory explanation for the relation of uric acid and the syndrome. This is of particular interest, since it has been suggested that the still disputed relationship between elevated uric acid and cardiovascular disease could be secondary to its association with obesity, dyslipidaemia, and hypertension. In addition, a number of epidemiological studies, in particular the one that has revisited the well-known Framinghan Heart Study, have shown that uric acid does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes (55). On the other hand, it has been suggested that high plasma urate concentrations may decrease the risk of Parkinson's disease, and they raise the possibility that interventions to increase plasma urate may reduce the risk and delay the progression of Parkinson's disease (56).

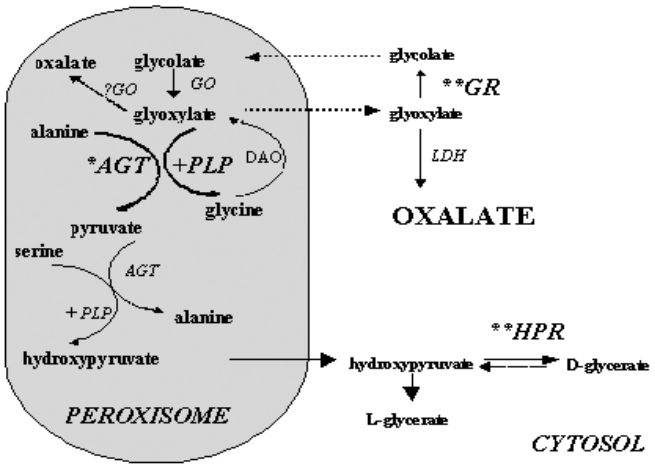
Administration of high daily doses of xylitol may provoke an increase in the serum uric acid concentration. This seems to result from an augmented purine biosynthesis, due to enhanced formation of ribose phosphate (see role of the hexose monophosphate shunt in providing sugars for nucleic acids). In the Bazzato's paper, where the daily dose of xylitol administered intraperitoneally was 150 grams, serum urate levels after 11 months of xylitol treatment were 9.1 mg/dL compared to 5.6 mg/dL before xylitol treatment (50).

Thus, considering that the normal plasma range of urate is 3.0-7.1 mg/dL (Scientific tables Geigy), xylitol treatment seems to modestly increase urate levels above the normal range. In the Buoncristiani experience, where the daily dose of xylitol administered intraperitoneally was 55 grams (almost 3 fold less than Bazzato), urate levels after years of xylitol treatment were slightly elevated compared to PD patients treated with glucose as an osmotic agent (52). However, such elevation remained within the normal range (Buoncristiani, personal communication).

Since we are planning to use lower amounts of xylitol compared to that used by Buoncristiani, potential elevation of uric acid in plasma is not an issue.

Oxalate: This compound is present in many plants, such as tea and green leafy vegetables, but very little is absorbed through the gastrointestinal tract. The colon is believed to be the major site of reabsorption. Oxalate is excreted exclusively in the urine as an end product of metabolism. There is no evidence to suggest that oxalate is metabolized in humans. Under normal conditions, urinary oxalate is derived primarily from glyoxalate, ascorbic acid, and dietary oxalate (**Figure 3**). Oxalate forms a wide variety of salts, the most important of which is calcium oxalate.

Figure 7.3. The metabolism of oxalate



The pathogenesis of oxalosis (primary and secondary) may be related to its poor water solubility. Indeed, nephrotoxicity of oxalate is believed to be related to a direct toxic effect on the renal tubules and interstitium, as well as to the development of oxalate stones.

Primary oxalosis is a multiorgan disease that results from calcium oxalate deposition in multiple tissues. Primary hyperoxaluria is a very rare congenital disease (incidence rate about 1.2/10,000,000 per year). It is inherited as an autosomal recessive trait and is characterized by the deficiency of the enzyme glyoxylate aminotransferase as in Type I primary hyperoxaluria and the enzyme D-glyceric dehydrogenase as in Type II (57).

Renal oxalate deposits are found primarily in the proximal tubules, and the natural history of this disease is the development of renal failure secondary to massive oxalate deposition in the kidneys. Renal transplantation is often complicated by recurrence of the disease, and a combined kidney and liver transplantation has been suggested by many to be the procedure of choice for primary hyperoxaluria Type I.

Secondary oxalosis is the result of excessive oxalate accumulation because of increased ingestion, increased production, or decreased excretion induced by exogenous factors. Two compounds, ethylene glycol (58) and methoxyflurane (59), that cause increased oxalate production, marked hyperoxaluria, and renal oxalate deposition, are well-known causes of acute renal failure. Renal insufficiency attributed to oxalate deposits has been reported with massive administration of vitamin C (60).

Recently, it has been reported a case of acute renal failure following xylitol infusion in a patient with previously unknown primary hyperoxaluria type 1 (61). A case of oxalate-induced lethal encephalitis (62) and fatal cerebrorenal oxalosis (63) have been reported in patients receiving parenteral infusion of various sugars (sorbitol, fructose, xylitol, etc) above the recommended dosages. There are few other cases of cerebro-renal oxalosis reported in the PubMed, though the casual relationship with xylitol infusion is quite dubious (presence of primary oxaluria, infusion of xylitol with other sugars including glucose, increased endogenous oxalate production in TPN patients, etc). In addition, according to Baxter Germany, no fatal cases resulting from Tutofusin OP X, a common infusion solution containing xylitol (50 grams per litre), has been reported so far (personal communication). Tutofusin OP X is in the market since several years and is largely used (half a million of bags sold per year). It should be noted that several other Companies containing xylitol alone or in combination with other ingredients (aminoacids, sugars, etc) have been registered in Germany as infusional products for total parenteral nutrition (Deltaselect, BBraun, Fresenius Kabi, Serag Wiessner).

From the metabolic standpoint, the formation of oxalate from xylitol as well as glucose is a minor pathway. Hauschildt et al have shown that in patients treated with parenteral infusion containing xylitol, the concentration of oxalate in the blood and the excretion of oxalate in the urine did not exceed the normal range in any patient (64). In addition, McWhinney et al. have shown no evidence of abnormal fluxes through the two-carbon pathway to oxalate, nor of hyperoxaluria in normal and recurrent stone formers subjects as related to xylitol infusion (65). Interestingly enough, an oral glucose load leads to a significant increase of calcium and oxalate excretion in the urine (66).

In the Bazzato's paper, where the daily dose of xylitol administered intraperitoneally was 150 grams, no clinical signs of calcium oxalate deposits, which would have worsened cerebral or residual kidney function, were noted throughout the treatment (50). In the Buoncristiani experience, where the daily dose of xylitol administered intraperitoneally was 55 grams (almost 3 fold less than Bazzato), no clinical signs of calcium oxalate deposits were noted and plasma oxalate levels were comparable to PD patients using glucose as the only osmotic agent (52).

Biocompatibility of peritoneal dialysis solutions containing glucose, xylitol and LC

LC and xylitol are extremely stable naturally occurring chemical compounds. For example, both compounds are thermally stable even at temperatures higher than those used to steam-sterilize infusional product (50, 67).

They are thermally stable in aqueous solutions buffered either in an acid, neutral or alkaline pH. LC or xylitol have safely been combined with many different nutrients for the development of total parenteral solutions and peritoneal dialysis solutions (PDS) (see also above).

As expected, preliminary stability studies conducted on the two PDS that we have planned to use for our clinical trial are demonstrated to be chemically and physically stable. The composition of our two PDS is the following: product code IPX15 contains glucose (0.5%), xylitol (1.5%) and LC (0.02%), and product code IPX07 contains glucose (0.5%), xylitol (0.7%) and LC(0.02%). In addition, both products contain the following salts: NaCl 5.786 g/L, CaCl2 · 2H2O 0.257 g/L, MgCl2 · 6H2O 0.102 g/L, sodium D/L-lactate 3.925 g/L. Both solutions are buffered at pH 5.5. The calculated osmolality of the two PD solutions are equivalent to the traditional 1.5% and 2.5%, glucose-based, PD solution. It is worth to mention that although xylitol and glucose are sugars, the former can be steam-sterilized in a wide range of pH without any risk of non-enzymatic oxidation, one of the main causes of glucose-mediated peritoneal damage (see also below). Indeed, reducing sugars such as glucose, oligosaccharide and polyglucose containing carbonyl groups in the sugar unit react with free amino groups of aminoacids and protein in a complex series of reactions known as the Maillard reaction. Since sugar alcohols or polyols such as xylitol do not participate in the Maillard reaction, xylitol represents a better alternative than glucose as an osmotic ingredient both from the manufacturing and biocompatibility standpoints (see also above).

Biocompatibility of Peritoneal Dialysis Solutions

The biocompatibility of a PDS may be defined as its capacity to leave the anatomical and functional characteristics of the peritoneum unmodified in time (68,69). In this context, challenging primary mesothelial cells with PDS is believed to be the gold-standard *in vitro* approach to assess the peritoneal biocompatibility of such solutions (68-70).

Mesothelial cells are specialized epithelial cells that line the serous cavities (pleural, pericardial, and peritoneal) and internal organs. Their primary function is to provide a nonadhesive frictionless protective barrier that facilitates movement of opposing tissues and organs within the serous cavities. Once considered to be passive cells, there is now compelling evidence to highlight their critical role in antigen presentation, inflammation, wound healing, and transport of fluids and cells across the serosal cavities (71,72). Mesothelial cells modulate the microcirculation by their ability to secrete vasodilators, such as prostaglandins and nitric oxide, or vasoconstrictors, such as endothelin. Furthermore, these cells elaborate fibrinolytic molecules to prevent fibrous adhesions have phagocytic properties that participate in defense against infections and are capable of synthesizing a plethora of macromolecules and peptides that contribute to the structural and functional integrity of the underlying basement membrane and the chemotactic gradient responsible for the recruitment of monocytes and neutrophils. Peritoneal mesothelial cells cultured in vitro possess the same immunohistochemical markers as peritoneal mesothelial stem cells, and thus they provide a pertinent in vitro model to study the effects of various agents and stimuli on cellular functions such as proliferation, viability, and protein synthesis (73).

It has soon become apparent that the currently used PDS are limited in terms of biocompatibility. Many studies have convincingly demonstrated the adverse effects of peritoneal dialysis solutions toward peritoneal membrane and peritoneal host defense (74–80). One of the aspects of peritoneal dialysis solutions that has been viewed as bioincompatible is the presence of glucose, which is added in high concentrations to most PDS as an effective osmotic agent. Both the development of "*diabetiform*" alterations in peritoneal ultrastructure in patients undergoing CAPD (81-84) and the impaired function of cells exposed to glucose-based PDS (78,85) have been linked either directly or indirectly to the use of glucose. These effects may be related to the metabolic action of glucose *per se*, the corresponding rise in osmolality, the accumulation of glycated proteins, and/or the formation of glucose degradation products (86).

At this regard, we have recently published two studies (87, 88) where we have examined the growth and function of primary rabbit peritoneal mesothelial cells cultured in the presence of various PDS containing either glucose alone, glucose and LC, xylitol and glucose, or xylitol, glucose and LC (see the exact composition of the various PDS and related acronyms in the Appendix). Glucose was present at two different concentrations (1.36 and 3.86 %, w/v). LC also was present at two different concentrations (0.05 and 0.2 %, w/v). Xylitol concentration, instead, was kept fixed at 1% (w/v). The biocompatibility of the PDS was evaluated according to various well-established growth and functional assays (68-70):

1. *Growth of mesothelial cell cultures*
2. *Secretion of phospholipids (PLPs) and phosphatidylcholine (PC) by mesothelial cells*
3. *Secretion of Prostaglandin E2 (PgE2) by mesothelial cells*
4. *Lactic dehydrogenase (LDH) release by mesothelial cells*

Highlights

Our study comparing the effects of PDS containing glucose alone with or without LC, and glucose and xylitol with or without LC on cultured mesothelial cells led to the following findings (85).

1. Mesothelial cells grew much better in PDS containing LC than in those PDS not containing it. In the glucose-xylitol PDS containing LC, mesothelial growth was higher than in those containing glucose and LC. Indeed, the lower the amount of glucose the better the growth. However, the presence of LC always showed an improvement of mesothelial growth.
2. Phospholipid secretion of mesothelial cells was much higher when LC was present in PDS. This is an important index of cell function, as phospholipids are essential for peritoneal physiology. Secretion of phosphatidlycholine, the most active mesothelial surfactant, was indistinguishable between cells cultured in medium with LC, (particularly XGC-2) and controls. Significantly lower secretion was observed with medium containing high glucose levels.
3. As a general index of cytotoxicity, LDH secretion by mesothelial cells was higher in media with PDS containing glucose alone and glucose plus xylitol than the respective PDS with LC.
4. Prostaglandin E2 secretion was significantly higher in media containing LC.

Collectively, these data suggest the addition of LC to various combinations of sugars render PDS more biocompatible. Overall, the best combination examined resulted to be the glucose-xylitol-LC.

Rationale for this study

The presented data clearly suggest the possibility of using solutions for peritoneal dialysis containing osmolar agents like xylitol and L-Carnitine. These solutions could not only significantly decrease the amount of glucose currently present in commercial PD solutions, but also to take advantage of the described metabolic properties of LC and xylitol, and to correct potential LC deficiency. A synergistic effect of the two compounds in improving glucose and lipid homeostasis in PD patients may conceivably be anticipated. The xylitol-glucose-LC based PD solution is also characterized by a more biocompatible profile than glucose-based ones. It is anticipated that a PD solution with such osmolar agents added to glucose, used for the nocturnal exchange, will lead to a significant reduction of glucose level in peritoneal dialysis solution during the night dwell, while preserving or even improving the depurative efficacy of the standard PD solution containing glucose 2.5%. The reduction of glucose level could be further enhanced if the PD solution with xylitol and carnitine will be used for the diurnal exchanges and a PD solution with icodextrin will substitute the standard PD solution containing glucose 2.5% for the nocturnal dwell.

8 STUDY OBJECTIVES

The aim of this study was to compare:

1) the effects of an experimental solution, named IPX15, containing glucose (0.5%), xylitol (1.5%) and L-carnitine (0.02%) as osmotic agents comparable to the standard 2.5% glucose PD solution, for the nocturnal exchange in 20 ESRD patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) (Group A) - or
2) the effects of an experimental solution, named IPX07, containing glucose (0.5 %) Xylitol (0.7 %) and L-Carnitine (0.02 %) as osmotic agents comparable to the standard 1.5 % glucose PD solution, for diurnal exchanges (1, 2 or 3 exchanges), combined with icodextrin for the nocturnal dwell, in 20 ESRD patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) (Group B)

8.1 Primary Objectives

1. To assess the safety and tolerability of the experimental solutions by:

- recording the incidence and severity of adverse events;
- recording a subjective questionnaire on the patient's perception of well being;
- monitoring the changes in routine blood biochemical and hematological parameters.

8.2 Secondary Objectives

1. To assess the effects of experimental solutions

- peritoneal clearances;
- peritoneal transport characteristics with respect to Day 0 and the follow-up period

2. To assess the effects of experimental solutions on peritoneum functionality by evaluation of changes in CA 125 and protein levels in ultrafiltrate

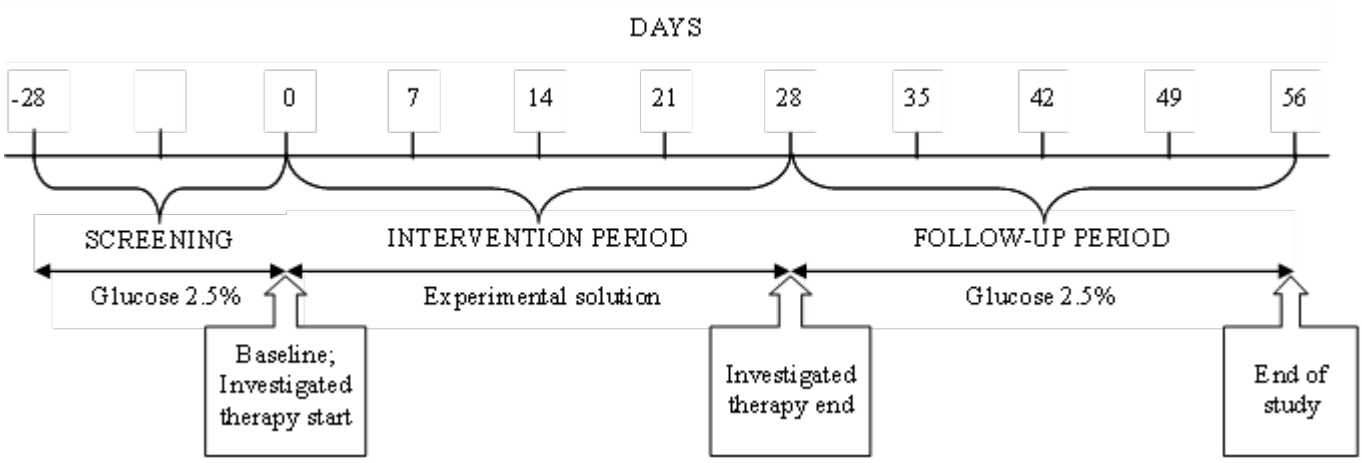
9 CLINICAL INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN-DESCRIPTION

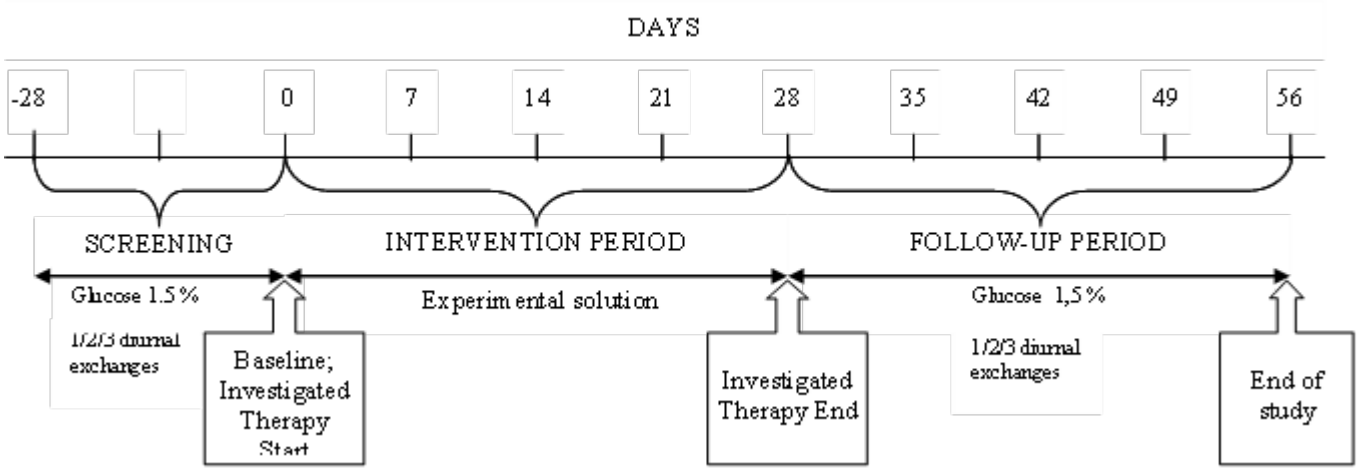
This was a phase II, prospective, investigational, open, multi-center study. The study will consist of three study periods, with a total duration of around 84 days (Figure 9.1).

Figure 9.1. Study design diagram

Group A



Group B



9.1.1 Screening and Baseline Evaluation

Subjects were screened for eligibility by the Investigator based on the inclusion and exclusion criteria in Section 9.3.1 and Section 9.3.2, and informed consent was obtained prior to performance of any study-specific procedure. A patient screening log for each center was kept in the eCRF. All subjects' demographics and medical history were documented.

The potential eligible patients entered a 4 weeks run-in period (screening period), for identification of eligible subjects. It comprised all clinical and laboratory assessments required to characterize the basal condition of patients in order to establish the accomplishment of inclusion criteria and the possible existence of exclusion criteria. For every patient, the investigators obtained a detailed medical/surgical history and perform an accurate physical examination, focusing on evaluation of concomitant diseases and prior or concomitant pharmacological therapies. At the end of the screening period (day 0), a careful analysis of eligibility was performed, including review of laboratory results and inclusion and exclusion criteria.

Depending on the previous peritoneal dialysis prescription, during the screening period, patients were assigned to Group A or Group B, with Group A, receiving standard solution with 2.5% glucose for the nocturnal exchange and Group B 1, 2 or 3 diurnal exchanges with 1.5% glucose solutions and one nocturnal exchange with icodextrin (Extraneal).

Before any study specific procedure was performed the Investigators obtained and documented the written informed consent from all potential subjects in accordance with current available ethical guidelines: GCP and principles originated from the Declaration of Helsinki for medical research on human subjects. Eligible pre-menopausal female subjects were requested to sign a declaration that they agree to use an efficient contraceptive method during the study.

9.1.2 Intervention period

The intervention period lasted 4 weeks. The subjects enrolled, included in the Group A received a bag with experimental solution (IXP15) for the nocturnal dwell, and subjects included in Group B received 1, 2 or 3 bags with the experimental solution (IXP07) for the daily exchanges and a bag with icodextrin solution for the nocturnal dwell. All subjects went to the study Center to undergo study visits. At each visit, the Investigator performed clinical and laboratory assessments, according to the study protocol. Patients' compliance to treatment, changes in concomitant diseases and medications, and adverse events occurrence were investigated.

9.1.3 Follow-up period

During the 4 weeks follow-up period, subjects returned to the use of standard solution with 2.5% glucose for the nocturnal exchange (Group A) or of the solution with 1,5 % glucose for diurnal exchanges (Group B) and went to the Center at days 42 and 56 to undergo study visits. During these visits, the investigators performed clinical and laboratory assessments, according to the study protocol, to evaluate the potential changes in peritoneal membrane function consequently to the use of experimental solution. Data regarding ultrafiltration volume, clinical parameters, concomitant medication, and occurrence of adverse events were recorded by the subject in his diary and were transcribed in the case report form by the investigator during a subsequent hospital visit.

9.1.4 Study end

For each subject, the study procedures ended with completion of the follow-up period (day 56).

Table 9-1 presents the schedule of assessment and procedure for the study. The protocol is provided in Appendix 16.1.1, and the sample CRF in Appendix 16.1.2.

Table 9-1. Schedule of Assessment

		SCREENING PERIOD		***INTERVENTION PERIOD***		***FOLLOW-UP PERIOD***	
Day		*-28*	*0*	*14*	*28*	*42*	*56*
Demographic data		✍					
Written informed consent		✍					
Medical and surgical history		✍					
Physical examination		✍					
Previous medication		✍					
Concomitant diseases		✍	✍	✍	✍	✍	✍
Concomitant medication		✍	✍	✍	✍	✍	✍
Clinical parameters[a)]		✍	✍	✍	✍	✍	✍
Pregnancy test		✍					
Eligibility criteria		✍	✍				
Functional parameters	Weekly urea KT/V		✍		✍		✍
	PET		✍		✍		✍
	Total creatinine clearance		✍		✍		✍
Carnitine level	Plasma		✍	✍	✍	✍	✍
	Urine		✍	✍	✍	✍	✍
	Dialysate		✍	✍	✍	✍	✍
Ultrafiltration	Nocturnal	✍	✍	✍	✍	✍	✍
	Total	✍	✍	✍	✍	✍	✍
Clinical chemistry [b)]		✍	✍	✍	✍	✍	✍
Hematology [c)]		✍	✍	✍	✍	✍	✍
Uric, lactic and oxalic acids		✍*	✍	✍	✍	✍	✍
Electrocardiogram (ECG)			✍		✍		
CA 125 / proteins in ultrafiltrate		✍	✍	✍	✍		✍
Bag accountability				✍	✍		
Adverse events				✍	✍	✍	✍
Subjective questionnaire			✍		✍		✍
End of study form							✍
Investigator’s confirmation							✍

9.1.5 Clinical Assessment

9.1.5.1 Efficacy

Outcome variables will be:

- daily ultrafiltration volume from baseline (i.e. day 0) to day 28 and 56;
- peritoneal equilibrium test from baseline to day 28 and 56;
- weekly total urea Kt/V from baseline to day 28 and 56;
- weekly total creatinine clearance from baseline to day 28 and 56.

9.1.5.2 Safety and tolerability

Outcome variables for safety and tolerability assessment will be:

- incidence and severity of adverse events during the intervention and follow-up periods;
- changes in the subjective questionnaire on the patient's perception of well being at days 28 and 56 as compared to baseline.
- occurrence of abnormal laboratory values at days 14, 28 and 56 as compared to baseline.
- change in CA 125 and protein levels in ultrafiltrate from baseline to day 28 and 56.

The parameters for safety and tolerability assessment are detailed in Section 8.

9.1.6. End of Treatment Assessment

An End of Treatment (study) assessment was arranged for subjects who completed the study.

9.2 DISCUSSION OF THE STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

This was a phase II, prospective, investigational, open, multi-center study. The study will consist of three study periods, with a total duration of 84 days.

The potentially eligible patients entered a 4 weeks run-in period (screening period) to identify eligible subjects. Depending on the previous peritoneal dialysis prescription, during the screening period, patients were assigned to Group A or Group B, with Group A, receiving standard solution with 2.5% glucose for the nocturnal exchange and Group B 1, 2 or 3 diurnal exchanges with 1.5% glucose solutions and one nocturnal exchange with icodextrin (Extraneal), continuing their previous PD prescription.

The intervention period lasted 4 weeks. The subjects enrolled, included in Group A received a bag with experimental solution (IXP15, equivalent in osmolarity to the glucose 2.5% solutions) for the nocturnal dwell, and subjects included in Group B received 1, 2 or 3 bags with the experimental solution (IXP07, equivalent in osmolarity to glucose 1.5% solutions) for the daily exchanges and a bag with icodextrin solution for the nocturnal dwell. These two dosing regimens are typical for patients in PD (CAPD) and consistent with previous prescriptions.

For all subjects, the Investigator performed clinical and laboratory assessments, according to the study protocol, to evaluate the potential changes in peritoneal membrane function consequently to the use of the experimental solution. Peritoneal dialysis performance test during the investigational treatment period were compared with results during the follow up period with glucose. The study parameters are typical for clinical trials in peritoneal dialysis, used in many previous studies.

During the 4 week follow-up period, subjects returned to the use of standard solution with 2.5% glucose for the nocturnal exchange (Group A) or of the solution with 1,5 % glucose for diurnal exchanges (Group B) and went to the Center on days 42 and 56 to undergo study visits. For each subject, the study procedures ended with completing the follow-up period (day 56).

In this study, the two treatment groups have been merged for statistical analysis.

The primary study objectives were to assess the safety and tolerability of the experimental solutions. The secondary objectives were to assess the performance of the peritoneal dialysis with the investigational product, specifically the peritoneal clearances and peritoneal transport characteristics with respect to Day 0 and the follow-up period, to ensure that the investigational product allows for effective peritoneal dialysis, at least non-inferior of glucose solutions. In this respect, due to the incomplete sample size enrolled (12 patients of the 80 planned), data from the two treatment groups (A and B) have been pooled to increase the informative value of the study. The tests used in the study (Kt/v, PET, Creatinine clearance and Ultrafiltration) show the effects of the PD product on peritoneal dialysis performance,

9.3 SELECTION OF STUDY POPULATION

Stable, End-Stage Renal Disease (ESRD) patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) without major cardiovascular comorbidities, regularly treated for at least three months before selection with a standard solution containing 2.5% of glucose for the nocturnal dwell (Group A) or regularly treated for at least one month before selection with 1; 2 or 3 diurnal exchange bag solution containing 1.5 % glucose combined with a nocturnal exchange with Extraneal, will be investigated.

9.3.1 Inclusion Criteria

Patients who met the following criteria were enrolled.

For inclusion in the study, patients of both genders must fulfill the following criteria, verified during the screening period:

1. Age ≥18 years;
2. Diagnosis of ESRD treated for at least three months with CAPD, as stated by the medical staff of the center;
3. Stable clinical condition within four weeks before screening period, certified by medical/surgical history, physical examination and laboratory exploration;
4. Hemoglobin level ≥9g/dL;
5. Absence of acute peritonitis and/or peritoneal catheter infection (either exit site or subcutaneous tunnel) episodes within three months before selection;
6. To understand and sign an informed consent form.

For patients who will be included in Group B, the following criteria must be fulfilled too:

7. Be treated with Extraneal (nocturnal exchange bag solution) for at least 1 month
8. Be treated with 1; 2 or 3 diurnal exchange bag solutions (solution bags with 1,5% glucose) and one nocturnal exchange bag solution with icodextrin (Extraneal).

9.3.2 Patient Exclusion Criteria

Patients who fulfilled any of the following criteria were not enrolled:

1. History of alcohol or drug abuse in the last six months before selection for the study;
2. Androgen therapy in the last six months before selection;
3. Active infections;
4. History of congestive heart failure stage III and IV NYHA;
5. History of major cardiovascular events like stroke, acute myocardial infarction, coronary or other arterial revascularization procedures in the last three months before selection;
6. Clinically relevant cardiac arhythmia;
7. Clinically relevant abnormalities of functional hepatic tests;
8. Therapy with L-carnitine or its derivatives in the last three months before selection;
9. Pregnancy, lactating women or female subjects of childbearing potential who do not use an effective method of contraception;

10. Presence of relevant chronic medical conditions that could suggest exclusion of patient from the study or could interfere with assessment of study parameters, especially if the life expectation is less than one year;
11. Participation in another clinical study within the past month;
12. Known allergic reactions to L-carnitine or xylitol.

9.3.3 Removal of Patients from Therapy or Assessment

The investigator could remove a patient from the study (subject withdrawal) if any of the following situations occur:

- Withdrawal of the subject's informed consent;
- Initiation of a disallowed concomitant therapy;
- Occurrence of an unexpected or serious/severe adverse event that could interfere with study evaluation or make its continuation inappropriate;
- Changes in the subject's clinical condition that could interfere with study evaluation or make its continuation inappropriate;
- Subject's non-compliance.

The investigational treatment had to be prematurely withheld and/or stopped also when:

- Logistical changes that would render the patient's participation to the planned study visits impossible, according to the study flow chart.

In any case of premature discontinuation from the study, the reason had to recorded in CRF as accurately as possible. In case of withdrawal due to a serious adverse event (SAE), the investigator had to be followed and registers the evolution of adverse event until its resolution.

In subjects withdrawn from the study, the investigator should make any reasonable effort to perform all the assessments scheduled for the last visit in order to conclude on the investigated treatment.

The study had to be discontinued if new information about the investigational product showed increased risk for the patient.

It was the investigator responsibility to follow-up with the patient for an adequate period (30 days) to evaluate the clinical condition, perform a laboratory examination, and survey the possible occurrence of adverse events even at a distance after the cessation of investigational treatment.

It was also recommended that these patients fulfill the follow-up period per study protocol after they were considered for the safety and tolerability analysis.

9.4 TREATMENT

9.4.1 Treatments Administered

During the 4-weeks Intervention Period all patients enrolled in the study received:

- GROUP A: the bag with experimental solution [product code IPX15, containing glucose (0.5%), Xylitol (1.5%) and L-Carnitine (0.02%)] used for the nocturnal exchange;

- GROUP B: the bag with experimental solution [product code IPX07 containing glucose (0.5%), Xylitol (0.7%) and L-Carnitine (0.02%)] used for the diurnal exchanges (1; 2 or 3), while a bag with icodextrin solution was used for the nocturnal exchange.

Both drugs were administered for peritoneal dialysis.

Batches of product code IPX15: 1905

Batches of product code IPX07: 2100460 and 1902

During the screening period, patients in Group A received standard solution with 2.5% glucose for the nocturnal exchange and Group B received their standard PD therapy (1,2 or 3 diurnal exchanges and one nocturnal exchange bag solution with icodextrin (Extraneal))

During the 4 weeks follow-up period, the subjects returned to the use of standard solution with 2.5% glucose for the nocturnal exchange (Group A) or of the solution with 1,5 % glucose for diurnal exchanges (Group B).

9.4.2. Identity of Investigational Products

IXP15 and IXP07 were supplied as sterile solution bags for peritoneal dialysis with the following composition:

ACTIVE COMPOUNDS:

	IPX15	**IPX07**
• L-carnitine (%)	0.02	0.02
• Xylitol (%)	1.5	0.7
• Glucose (%)	0.5	0.5
• Sodium (*mmol/L*)	134	134
• Calcium (*mmol/L*)	1.75	1.75
• Magnesium (*mmol/L*)	0.5	0.5
• Chloride (*mmol/L*)	103.5	103.5
• L-lactate (*mmol/L*)	35	35
• pH	5.5	5.5

The primary packaging was a single chamber polypropylene bag containing the experimental solution. The solution bags were provided with a pre-assembled transfer set for peritoneal dialysis, with an empty polypropylene bag for collection of effluent, for each peritoneal dialysis and a Luer-Lock connection to the patient, consistent with Twin-Bag Baxter. Each bag with the transfer set and the empty bag for effluent collection were over-wrapped with formable film/envelopes before sterilisation.

All study medications were labelled according to the EU Regulation (Eudralex Vol 4 Annex 13, Investigational Medicinal Products).

IXP15 and IXP07 batches were manufactured and labelled according to GMP by Galenica Senese, Via Cassia Nord, 351 – 53014 Monteroni d'Arbia (Siena) Italy.

The bags were stored at temperature between 4°C and 30°C, protected from light, in a secure, lockable place with limited access only for persons involved in the study.

IXP15 and IXP07 were provided to investigators free of charge. The icodextrin solution bags required for the Group B were also provided to Investigators free of charge by the Sponsor.

9.4.3 Method of Assigning Patients to Treatment Groups

Potentially eligible patients treated with standard solutions with 2.5% glucose for the nocturnal exchange or standard PD therapy [(1, 2 or 3 diurnal exchanges with 1.5% glucose and one nocturnal exchange with icodextrin (Extraneal)] entered a 4 week run-in period (screening period), dedicated to the identification of eligible subjects. It comprised all clinical and laboratory assessments required to characterize the basal condition of patients in order to establish the accomplishment of inclusion criteria and the possible existence of exclusion criteria. During the screening period patients continued their prescriptions before the study.At the end of the screening period (day 0), a careful eligibility analysis was performed.

Eligible patients who received 2.5% glucose for the nocturnal exchange were assigned to Group A, and patients who received 1,2 or 3 diurnal exchanges with 1,5% glucose and one nocturnal exchange with icodextrin (Extraneal), were assigned to Group B. Assignment to the study treatment was not randomized.

9.4.4. Selection of Doses in the Study

Eligible patients who were receiving peritoneal dialysis with 2.5% glucose for the nocturnal exchange before entering study were assigned to Group A [receiving IPX15 containing glucose (0.5%), Xylitol (1.5%) and L-Carnitine (0.02%)], and patients who were receiving PD therapy with 1,2 or 3 diurnal exchanges with 1,5% glucose and one nocturnal exchange bag solution with icodextrin (Extraneal) before entering the study were assigned to Group B [receiving IPX07 containing glucose (0.5%), Xylitol (0.7%) and L-Carnitine (0.02%)].

9.4.5 Selection and Timing of Dose for Each Patient

Eligible patients who were receiving peritoneal dialysis with 2.5% glucose for the nocturnal exchange before entering the study were assigned to Group A, receiving IPX15 for nocturnal exchanges with the same schedule before entering the study, and patients who were receiving PD therapy with 1,2 or 3 diurnal exchanges with 1,5% glucose and one nocturnal exchange bag solution with icodextrin (Extraneal) before entering the study were assigned to Group B receiving IPX07 with the same schedule of before entering the study.

9.4.6 Blinding

Not applicable.

9.4.7 Prior and Concomitant Therapy

The information regarding concomitant pharmacological treatment includes data concerning the drugs regularly received during the last three months before enrollment (recorded in the section “Previous Medication” from CRF) and data concerning therapies received at the moment of inclusion into the study (recorded in the section “Concomitant Medication” from CRF).

Any pharmacological therapy administered for pathology unrelated to the study, considered necessary for the patient's well being and that does not interfere with the investigational product, may be given at the discretion of the investigator or personal physician of the patient. All these drugs must be recorded in the appropriate section of CRF, noting the dosage, date and duration of administration in correlation with the indication.

If, after starting the intervention period of the study with the investigational solution, the administration of another drug becomes necessary for any symptom/sign, this therapy had to be reported in the section "Concomitant medication" from CRF.

Changes in dosage of any concomitant medications decided by the investigator must be recorded in the original files of the medical institution where the patient is treated (hospitalization files, dialysis files, or similar) and in the CRF.

If the patient was treated with L-carnitine or a derivative, these drugs must be stopped at least three months before selection for the study. The change of the dialysis bag for the nocturnal exchange is disallowed during the entire study period.

Allowed concomitant pharmacological therapy

Concomitant therapies within the following drug categories were allowed:

- anti-hypertensives, coronary vasodilators, tonicardiac drugs;
- aspirin, antithrombotic drugs and coumarins anticoagulants;
- erythropoiesis-stimulating agents, intravenous iron;
- contraceptives.
- any drug considered necessary for pathology unrelated to the study, as judged by the investigator or personal physician of the patient, that does not interfere with the investigational product.

The therapeutic regimen of ESRD patients on CAPD was considered stable if the dosage of any drugs used was not modified in relation to the follow-up of the laboratory parameter values. Therefore, the term "therapeutic stability" refers to the stability of the patient's clinical status rather then to the absence of dosing changes. Hence, the dose adjustment of any drug required for the treatment of studied pathology was not a reason for the non-inclusion of a patient in the study or for his premature discontinuation. These changes had also to be recorded in the subject's Case Report Form.

9.4.8 Treatment Compliance

The investigators were requested to explain to the patients the importance of regular use of the bag with the investigational solution, and the patient had to keep accurate evidence of its use in his regular Peritoneal Dialysis Diary.

The investigator should record in the corresponding section of the CRF the observations on prescription and the calculation of compliance with treatment.

The assessment of compliance to treatment, defined as the patient's adhesion to the prescribed dosage (ratio between the number of bags used and the number of bags that had to be used), was performed at the end of the study. The assessment of compliance to treatment was used for the statistical evaluation of results, with patients being considered:

- compliant (adherent) – patients who have used at least 80% of the bags with the investigational solution;
- non-compliant (non-adherent) – patients who have used less than 80% of the bags with the investigational solution.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measures Assessed and Schedule of Study Events

Since the study had an explorative character, no primary and secondary efficacy parameters were identified.

The following efficacy parameters were assessed during the study:

1. Peritoneal Equilibrium Test (PET);
2. weekly total urea Kt/V (KT/V);
3. weekly total creatinine clearance (CrCL);
4. Peritoneal ultrafiltration (UF);

PET, KT/V, CrCL and UF were performed according to standardised clinical procedures.

The efficacy parameters have been assessed at following times:

	SCREENING PERIOD		***INTERVENTION PERIOD***		***FOLLOW-UP PERIOD***	
Day	*-28*	*0*	*14*	*28*	*42*	*56*
Weekly total urea Kt/V		✍		✍		✍
PET		✍		✍		✍
Weekly total creatinine clearance		✍		✍		✍
Total peritoneal ultrafiltration	✍	✍	✍	✍	✍	✍
Nocturnal ultrafiltration	✍	✍	✍	✍	✍	✍

Carnitine absorption, distribution and metabolism

Free carnitine and its acyl-derivatives levels in blood, urine and peritoneal effluent were assessed at different time during the study.

9.5.2 Safety Measurement

Outcome variables for safety and tolerability assessment were:

- incidence and severity of adverse events during the intervention and follow-up periods;
- changes in the subjective questionnaire on the patient's perception of well being at days 28 and 56 as compared to baseline.

- occurrence of abnormal laboratory values at days 14, 28 and 56 as compared to baseline.
- change in CA 125 and protein levels in ultrafiltrate from baseline to day 28 and 56.

9.5.2.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject who received a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An adverse event can be any unfavorable and undesirable medical condition: sign (including an abnormal laboratory finding), symptom or disease (including the worsening of a pre-existing medical condition) temporally associated with the use of a medicinal product, whether or not considered causally related to the medicinal product.

An Adverse reaction (side effect) is defined as any noxious and unintended response to a medicinal product related to the normal dosage used in humans for prophylactic, diagnostic or therapeutic purposes or for changing a physiological function. The phrase "response to a medicinal product" means that a causal relationship between the medicinal product and the adverse event is at least reasonable possible, i.e. the relationship cannot be ruled out. Therefore, those reactions that "doubtfully" correlate with the investigated medicinal product should be considered side effects as well as those for which there are not indications for establishing correlation at the moment of its appearance.

An Unexpected Adverse Event or Reaction is the adverse event/reaction that was not mentioned in the informative materials regarding the investigated product (for example: Investigator's Brochure for a product in experimental period; abstract of the product's characteristics for a product already on market).

Any adverse event, whether expected or unexpected, that meet one or more of the following criteria/outcomes, was classified as Serious and reported (see below).

a. results in patient's death;
b. is immediately life-threatening;
c. requires in-patient hospitalization or prolongation of existing hospitalization;
d. results in persisting or significant disability or incapacity;
e. is a congenital abnormality or birth defect:
f. Other medical condition with significant hazard according to the investigator's opinion.

Each adverse event had to be classified by the Investigator as SERIOUS or NON -SERIOUS. However, symptoms of underlying disease (as described above) are not to be considered adverse events in this study.

- the term "severe" (or relevant) describes the intensity of an event (like mild, moderate or severe myocardial infarction) and such an event may be of minor medical relevance (like a severe headache);
- the term "serious" is based on its outcome and is defined by the patient's exposure to major risks, inclusive life-threatening (see above). The seriousness of an event defines the obligation of notifying the Legal Authorities. This type of adverse reactions must be immediately reported to the Legal Authorities as specified in the current accepted guidelines.

Reporting procedures for Serious Adverse Events

In case of a Serious Adverse Event, the investigator must additionally document all related data from AE section in CRF to the SERIOUS ADVERSE EVENT FORM, consisting of 5 pages and containing a detailed description of the event and its outcome. This form, together with a completed expedition form, must be sent by fax within 24 hours of discovery or notification of event to:

Sintesi Research S.r.l. società unipersonale
Safety Office
E-mail.: +39-02-3489198298; Fax: +39-02-97374301

Iperboreal Pharma S.r.l will request additional information, if necessary for the evaluation of SAE. In response, the investigator must send a completed SAE/ADR CLARIFICATION FORM or a FOLLOW-UP SAE FORM. When necessary, accompanying medical documents (i.e. copies of hospital or autopsy reports) and relevant pages from CRF should also be sent.

The SAE form must be sent together with a transmission file (FILE FOR SAE FORM TRANSMISSION) that contain the name of investigator and its contact address (fax, phone, e-mail) and will be provided with the Investigator's File.

Reporting procedures for non-serious adverse events

Non-serious adverse events will be identified at all study visits and will be recorded in the appropriate section of CRF, each event on a separate page. A brief description of the event with: dates of onset and resolution, intensity degrees, frequency of occurrence, treatment required, studied product action taken, outcome, causality/relationship with investigational product and whether the event is classified as serious must be provided.

Each adverse event was graded to describe its intensity according to the following Severity scale:

- mild: an AE that does not interfere with usual activities.
- moderate: an AE that interferes with usual activities.
- severe: an AE that is intense or debilitating and interferes with usual activities.

The investigator had to assess assess the causality/relationship between the investigational product and the AE, using the following categories:

- definitely related;
- probably related;
- possibly related;
- unlikely related;
- not related.

The completed AE page will be taken by the study monitor the first monitoring visit after the end of AE and will be given to the responsible person with study Data-base.

When, during the study, a non-serious adverse event has an unfavorable evolution toward serious adverse event in the investigator's opinion, the recommended procedures for this category must be followed.

9.5.2.2 Laboratory and Other Assessments

The patient's tolerability to treatment was evaluated by measurements of the main laboratory parameters from drawn blood samples, in order to assess the safety and tolerability of the experimental solution used in this study.

The following parameters were measured:

- Clinical chemistry: serum sodium, potassium, calcium, phosphorus, total protein, albumin, GOT (AST), GPT (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, fasting glucose, total cholesterol, HDL-cholesterol,
- LDL-cholesterol triglycerides, blood urea nitrogen (BUN), creatinine, C-Reactive Protein (CRP);
- Haematology: hemoglobin, hematocrit, RBC count, reticulocytes, WBC count and WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count;
- CA 125 and protein levels in the peritoneal effluent after the nocturnal exchange.
- Uric acid, lactic acid and oxalic acid.

The following table presents the timing of the laboratory examinations:

	SCREENING PERIOD		***INTERVENTION PERIOD***		***FOLLOW-UP PERIOD***	
Day	*Day-28*	*Day 0*	*Day 14*	*Day 28*	*Day 42*	*Day 56*
Clinical chemistry	✍	✍	✍	✍	✍	✍
Hematology	✍	✍	✍	✍	✍	✍
CA 125 / proteins in ultrafiltrate	✍	✍	✍	✍	✍	✍
Uric acid, lactic acid and oxalic acid	✍	✍	✍	✍	✍	✍

Blood samples will be drawn in the morning, after at least 8 hours of fasting.

All the assessments will be performed locally. The results will be expressed in Standard International Units or in conventional units.

Laboratory Responsible will provide the normal range for each analyte, the description of the equipment and certifications relating to validation and quality assurance controls

A supplementary assessment of tolerability has been conducted through a self-administered subjective questionnaire on the patient's perception of well-being at baseline, day 28, and day 56.

Table 9.5.2.3 Subjective questionnaire on the patient's perception of well being.

A subjective questionnaire on patient perception of well-being was self administered on day 0, day 28, and day 56, and included 15 items: nausea, asthenia, lack of appetite, constipation, diarrhea, stomach pain, muscle aches, muscle cramps, itching, breathing difficulties, chest pain, fatigue, feeling faint, tingling in the hands and feet, problems with the peritoneal catheter. Each item was given a score that ranged from 0 to 5, based on the intensity of the symptom: score 0 corresponded to slight intensity, score 5 to severe intensity. The higher the global score, the worse the perception of well-being.

Figure 9.2. Subjective Questionnaire

1 Compared to a month ago, how would you rate your current state of health?

Much better now than a month ago	Slightly better now than a month ago	About the same as a month ago	Slightly worse now than a month ago	Much worse now than a month ago
□1	□2	□3	□4	□5

2 Over the past four weeks, how much did each of the following symptoms bother you?

	Not at all	A little	Enough	A lot	Very much
• Nausea	□1	□2	□3	□4	□5
• Lack of Appetite	□1	□2	□3	□4	□5
• Constipation	□1	□2	□3	□4	□5
• Diarrhea	□1	□2	□3	□4	□5
• Stomachache	□1	□2	□3	□4	□5
• Muscle pain	□1	□2	□3	□4	□5
• Muscle cramps	□1	□2	□3	□4	□5
• Itching	□1	□2	□3	□4	□5
• Shortness of breath	□1	□2	□3	□4	□5
• Chest pain	□1	□2	□3	□4	□5
• Fatigue	□1	□2	□3	□4	□5
• Feeling faint, diziness	□1	□2	□3	□4	□5
• Numbness, tingling in hands and feet	□1	□2	□3	□4	□5
• Problems with the peritoneal catheter	□1	□2	□3	□4	□5

9.5.3 Appropriateness of Measurements

The justification for use of efficacy endpoints is provided in Section 9.2. All efficacy and safety measurements described are commonly used in this type of study, and are generally recognised as reliable, accurate, and relevant..

9.5.4 Efficacy Variable(s)

Since the study had an explorative character, no primary and secondary efficacy parameters were identified. The following efficacy parameters were assessed during the study:

1. Peritoneal Equilibrium Test (PET);
2. weekly total urea Kt/V (KT/V);
3. weekly total creatinine clearance (CrCL);
4. ultrafiltration (UF);

The weekly total urea Kt/V (KT/V) was determined according to the following formula:

$$Residual\ renal\ KT/V\ [ml/min] = \frac{Urea\ 24h\ urine\ [mg/dl]}{Urea\ serum\ [mg/dl]} * \frac{Volume\ 24h\ urine\ [l] * 1000}{1440\ [\text{min}\ in\ 24h]}$$

$$Residual\ weekly\ \frac{KT}{V} = \frac{Residual\ renal\ KT/V\ [ml/min] * 1440 * 7}{weight\ [kg] * 0.6\ or\ 0.55\ [men\ or\ women] * 1000}$$

$$Dialysate \frac{KT}{V} = \frac{\frac{Urea\ 24h\ dialysate\ [mg/dl]}{Urea\ serum\ [mg/dl]} * Volume\ 24h\ dialysate * 7}{weight\ [kg] *\ 0.6\ or\ 0.55\ [men\ or\ women]}$$

$$\boldsymbol{Total\ weekly \frac{KT}{V}} =\ residual\ weekly\ \frac{KT}{V} +\ Dialysate \frac{KT}{V}$$

A standard Peritoneal Equilibrium Test (PET) was used to assess PM transport characteristics. It consisted of a 4 h dwell with 3.86% glucose during which period we collected dialysate samples at times 0, 120, and 240 min, while a blood sample was taken at 240 min. All blood and dialysate samples were then analyzed within 24 h. The dialysate's creatinine concentration was corrected for interference with glucose in the effluent.
The PET was determined according to the following formula:

- PET Creatinine = concentration in the dialysate/ concentration in the plasma
- PET Glucose = concentration in the dialysate/ concentration in the dialysate at t0

A description of PET has been reported by La Milia 2007 (91).

The Peritoneal Ultrafiltration was determined according to the following formula:
UF = Volume of liquid extracted from the peritoneum subtracted of the initial volume administered to the patient

Creatinine clearance (CrCL) was performed according to standard clinical procedures.

9.5.5 Drug Concentration Measurements

Serum, urine, dialysate Carnitine concentrations

In the last day of the Screening Period (day 0), a venous blood sample (5 mL) were drawn in the morning, after nocturnal dwell, concomitantly with a peritoneal effluent sample (10mL) and an urine sample (10mL) from the 24-hour urine collection, for the assessment of basal levels of total carnitine (TC), free carnitine (FC) and acetyl-carnitine (AC).

At the next nocturnal exchange (Intervention Period day 1), the patient begun the administration of the first experimental solution containing glucose, xylitol and carnitine.

The absorption, distribution and metabolism of L-carnitine were evaluated from the following examinations:

Blood samples	*Day 0, 14, 28, 42, 56*	At the end of the nocturnal dwell after the peritoneum was emptied
Dialysate samples	*Day 0, 14, 28, 42, 56*	A sample of peritoneal dialysate (10 mL) was collected from the effluent obtained after nocturnal dwell
Urine samples	*Day 0, 14, 28, 42, 56*	A sample of urine (10 mL) from the 24-hour urine collected during the day before hospital visit was analyzed

Blood samples (5 ml) were centrifuged at 1200g for 10 minutes and the plasma aliquot will be used for carnitine levels determination (90).

The plasma, urine and peritoneal effluent samples were stored at -20°C and transported on dry ice to Central Laboratory for determination.

The samples were analyzed by Biochimica Analitica Laboratory – Dept Scienze Biomediche of Centro Studi sull'Invecchiamento (Ce.S.I.) – Università degli Studi di Chieti e Pescara (Via Colle dell'Ara, Chieti Scalo). The material of use (provided free of charge by Sponsor) and the methodological procedures were described in a document specially prepared for the study.

Laboratory Responsible provided the normal range for each analyte, the description of the equipment and certifications relating to validation and quality assurance controls.

9.6 DATA QUALITY ASSURANCE

Accurate and reliable data collection was assured by verification and cross-check of the CRFs against the patient's Investigator's records by the study monitor (100% source document verification was performed), and the maintenance of a drug-dispensing log by the center.

A comprehensive validation check program was used to verify the data, and discrepancy reports were generated accordingly for resolution by the Investigator. Throughout the study, the Study Management Team reviewed data according to the Edit Specifications Document as described in the Data Management Plan (provided in Appendix 16.1.9).

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical Analysis Plan

Details of the Statistical Analysis Plan (SAP) are contained in the Study Protocol.

9.7.1.1 Analysis Sets

Study population consists of all subjects in the study database who completed treatment.

All patients who use at least one bag with the experimental solution or with the standard solution were included in the safety analysis.

9.7.1.1.1 Definition of Protocol Violation

None

9.7.1.2 Interim Analysis

None

9.7.1.3 Statistical Methods

Considering that the purpose of these analyzes is purely exploratory and that the number of patients involved is largely below the number foreseen in the study protocol, the analysis was conducted with a "non-parametric" approach, using the "Wilcoxon Matched- Pairs Signed-Ranks test" and without any correction of the "p-value" for multiple comparisons.

9.7.1.4 Subject Disposition

The number of subjects screened and enrolled, and the number of subjects who completed/discontinued were summarised using frequencies and percentages for all subjects.

9.7.1.5 Efficacy Analyses

Efficacy analysis compared the effect of the "experimental solution" as osmotic agents with the standard PD solution used in the follow-up period (from day 28 to 56).
All analyses have been performed using SAS (Version 9.4)
For all outcome variables (Peritoneal Equilibrium Test; weekly total urea Kt/V; weekly total creatinine clearance; ultrafiltration) values have been compared between the intervention period (from day 0 to day 28) and the follow-up period (from day 28 to day 56) using the "Wilcoxon Matched- Pairs Signed-Ranks test" and without any correction of the "p-value" for multiple comparisons.
As additional analysis, deltas were computed between day 28 and day 0, relatively to the intervention period, and between day 56 and day 0, relatively to the follow-up period. For each evaluated period a one-sample t-test has been performed to test differences from zero of the delta variables. For each variable, deltas have been compared between the two periods, using the "Wilcoxon Matched- Pairs Signed-Ranks test" and without any correction of the "p-value" for multiple comparisons.

9.7.1.6 Safety Analyses

9.7.1.7.1 Extent of Study Drug Exposure

The doses administered by the patients have been collected. Also, the information on exposure to study medication was listed for all subjects.

10.7.1.7.2 Adverse Events

All patients who use at least one bag with the experimental solution or with the standard solution were included in the safety analysis. Safety analyses included tabulation of type and frequency of adverse events. Any serious adverse event was reported with a comprehensive description.

Adverse Events were coded by MedDRA version 23.1 All AEs were summarised by MedDRA body system and preferred term.

9.7.2 Determination of Sample Size

The sample size has been calculated on the base of the following hypothesis about a subjective questionnaire on the patient's perception of well being.

The null hypothesis (H0) presuppose that the state of health measured at the end of both treatments (experimental (day 28) and standard treatment (day 56)) remains unchanged, whereas the alternative hypothesis (H1) presupposes an improvement in the state of health at the end of the experimental treatment of at least one point within the 1 to 5 scale.

Given $\Delta=1$, α, β equal to 0.05 and 0.20 respectively, with a standard deviation of the difference Δ equal to 1.5, at least 40 patients (20 Group A + 20 Group B) had to be enrolled so that 80 treatments (40 for Group) will be administered (each patient will be in fact treated first with the experimental treatment and then with the standard treatment).

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The original protocol is dated 20 July 2010 (Protocol Version 3). Protocol was amended (Amendment 1), Protocol Version 4 dated 28 April 2011. Please note that the documentation of the authorization by central authority (AIFA) of the original protocol (Version 3), and Amendment 1 (Protocol Version 4) is not available (however, authorizations by Ethical Committees have been found).

Study remained in stand-by until Protocol Amendment 2 (Protocol Version 5) of 31 January 2018, which was approved by AIFA and Ethical Committees. (changes of manufacturing site, labelling, use of eCRF, change of CRO and site list)

First patient was enrolled on November 13, 2019 (Patient 01-001).

Protocol Amendment 3 (Protocol Version 6) is dated 1 April 2020 (changes of site list, drug accountability, central labs, pharmacovigilance responsible).

The study protocol, amendments and amendment rationale documents are provided in Section 16.1.1.

10 STUDY PATIENTS

10.1 Disposition of Subjects

Three centers screened 15 subjects and 13 were enrolled, between October 2019 and December 2021. One subject was lost to follow-up and did not completed treatment (patient 01-010 in Group A discontinued before day 28 visit).

Overall, 12 subjects received trial treatment: 6 (50%) the treatment Group A [IPX15 containing glucose (0.5%), Xylitol (1.5%) and L-Carnitine (0.02%) administered for during the nocturnal exchange] and 6 (50%) the treatment Group B [IPX07 containing glucose (0.5%), Xylitol (0.7%) and L-Carnitine (0.02%) administered for the 1, 2 or 3 diurnal exchanges]. All 12 subjects completed the treatment

A summary of patients' disposition is provided in Table 10-1, Figure 10-1, and Listing 16.1.1. Enrollment by Investigator is presented in Table 10-2

The database freeze from August 2023 was used for the analysis.

Table 10-1. Subjects disposition – All Subjects

Disposition of patients	Total N. patients
Subjects Screened	15
Subjects not enrolled	2
Subjects Enrolled	13
Subjects completed study	12
Subjects discontinued the study	1*
Subjects with protocol deviations	-
Subjects with major protocol violations	-

* Subject 01-010 lost to follow up before day 28 visit (during run-in: the subject did not receive treatment)

Figure 10-1. Subject disposition

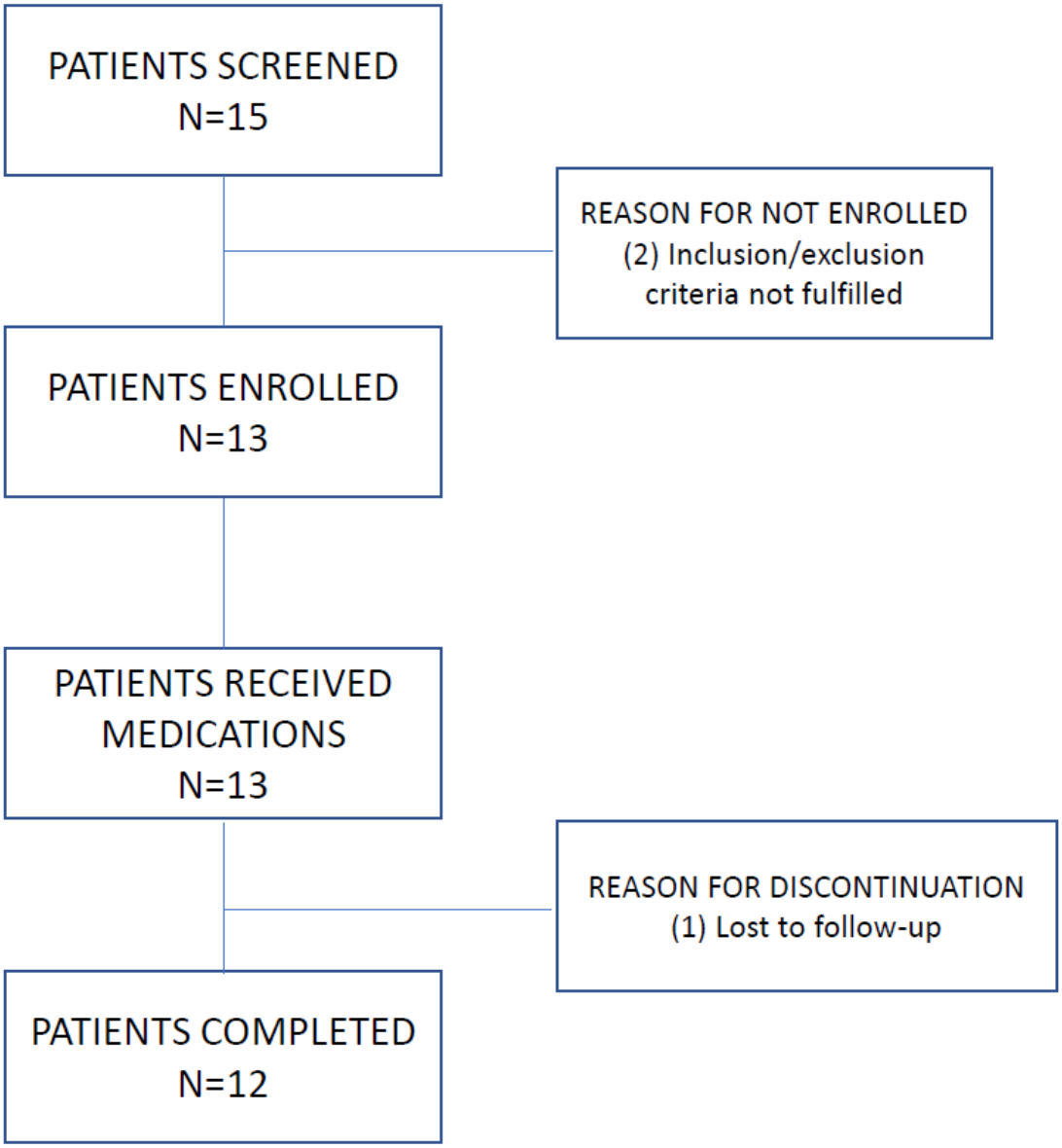


Table 10-2 Enrollment by Investigator

Center number	Principal Investigator	Center name	N. of Subjects
01	Mario Bonomini	Ss. Annunziata Hospital / University "G. D'Annunzio", Chieti	11
02	Loreto Gesualdo	Policlinico Bari	2
03	Giuseppe Grandaliano	IRCCS A. Gemelli	-

.10.2 Protocol Deviations

There were no major protocol violations. The following protocol deviations were recorded for this study. They were all considered Minor.

- Patient 01-001 (Group B): IPX15 (study medication for group A) was incorrectly delivered to the patient. However, the drug was promptly substituted with the correct study medication IPX07.The patient has not administered any dose of incorrect study medication.
- Patient 01-011 (Group A): Plasma samples for oxalate were not taken in the last two visits.
- Patient 05-001 (Group B): LDL, HDL, CA125 and total proteins in dialysate were not tested at screening. PET, KT/V, ECG and 24 h proteinuria at baseline were performed with 2 days delay. Visit at day 42 was performed with 6 days delay due to COVID situation. Due to his health condition, patient was unable to attend to visit at day 56 in the established date. In agreement with the PI the examinations planned for this visit were performed at first control visit (PET was not performed).
- Patient 05-002 (Group B): Visit at day 42 was performed with 4 days delay and visit at day 56 was performed with 9 days delay due to COVID situation.

11 EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

The analysis populations of the protocol included all subjects in the study database who completed treatment.

Study enrolled stable End-Stage Renal Disease (ESRD) patients on Continuous Ambulatory Peritoneal Dialysis (CAPD), regularly treated for at least three months before selection with a standard solution containing 2.5% of glucose for the nocturnal dwell (Group A) or regularly treated for at least one month before selection with 1, 2 or 3 diurnal exchange bag solution containing 1.5 % glucose combined with a nocturnal exchange with Extraneal (Group B).

The potential eligible patients were assigned to Group A or Group B and entered a 4 weeks run-in period (screening period), dedicated to the identification of eligible subjects. During the screening period, Group A received standard solution with 2.5% glucose for the nocturnal exchange and Group B received their standard PD therapy (1,2 or 3 diurnal exchanges and one nocturnal exchange bag solution with icodextrin (Extraneal)).

The intervention period lasted 4 weeks. The subjects included in the Group A received a bag with experimental solution (IXP15) for the nocturnal dwell, and the subjects included in the Group B received 1, 2 or 3 bags with the experimental solution (IXP07) for the daily exchanges and a bag with icodextrin solution for the nocturnal dwell.

At the end of treatment, all patients entered a 4 weeks follow-up period, with use of standard solution 2.5% glucose for the nocturnal exchange (Group A) or of the solution with 1,5 % glucose for diurnal exchanges (Group B).

From the overall 15 screened subjects, 13 were enrolled (1 subject was lost to follow up before day 28 visit) and 12 completed treatments according to the study protocol.

Analysis sets and reasons for exclusion are summarized, by sequence, in Table 11-1 below.

Table 11-1. Summary of Subject disposition

Disposition of patients	Run-in period (4 weeks)	Treatment period (4 weeks)		Follow-up period (4 weeks)
		Group A (IXP15)	Group B (IXP07)	
Subjects Screened	15	-		-
Subjects not enrolled	2	-		-
Subjects Enrolled	13	7	6	12
Subject received treatment	12	6	6	12
Subjects completed treatment	12	6	6	12
Subjects discontinued study	1*	1*	-	-
Safety Population	12	6	6	12
Efficacy Population	12	6	6	12

* Subject 01-010 lost to follow up before day 28 visit (during run-in: the subject did not receive treatment)

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics

Demographic and baseline characteristics are summarised in Table 11-2 below, and provided by subject in Listings 16.2.1.

Table 11-2. Demographic and Baseline Characteristics

	(N=13)
Age (years)	
• Mean	66.62
• Std	11.38
• Median	67
• Min - Max	37-82
Sex	
• Male	10 (76.9%)
• Female	3 (23.1%)
Race	
• White	12 (100%)
Height [cm]	
• Mean	169.54
• Std	8.15
• Median	170
• Min - Max	155 - 186
Weight [kg]	
• Mean	79.98
• Std	15.03
• Median	82
• Min - Max	51 - 100

Medical History

Investigator terms for medical and surgery history are provided in Listing 16.2.2.

Previous and Concomitant Medications

Details on previous and concomitant medications are provided in Listing 16.12.

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Peritoneal dialysis was administered at home by patients/caregivers and data on drug accountability collected. Patients' exposure to the study drug is discussed in Section 12.1. The exposure to the drug is also supported by plasma, urine and dialysate determinations of carnitine and derivative which are reported in Listing 16.14.1-2, Listing 16.151-2, Listing 16.16.1-2.

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.4.1 Analysis of Efficacy

At the time of statistical analysis, 12 subjects were included in the efficacy analysis as outlined in Table 11-1 and Figure 10-1. A total of 12 subjects completed both periods (treatment period and follow-up period).

Efficacy analysis was performed according to study protocol V6 dated 1 April, 2020 (Amendment 3).

However, due to the fact that the purpose of these analyses is purely exploratory and that the number of patients involved is largely below the number foreseen in the study protocol, the analysis was conducted with a "non-parametric" approach, using the "Wilcoxon Matched- Pairs Signed-Ranks test" and without any correction of the "p-value" for multiple comparisons.

As regards the comparison between the two treatment periods (Period 1: "Intervention Period" and Period 2: "Follow up Period"), the changes from Day 0-Day 28 and Day 28-Day 56 were compared, respectively. Results are summarized in Tables 14-5 to 8.

11.4.1.1 Weekly Total Urea Kt/V

KT/V urea data for each patient at day 0 (end of run-in with glucose PDS), day 28 (end of treatment with the investigational product) and day 56 (end of follow-up period) are reported in Table 11-3.

There are no statistically significant differences for the changes in Kt/V between day 0 and day 28 [Δ = 0.106 ± 0.239; P=0.1694], between day 28 and day 56 [Δ = -0.049 ± 0.219; P=0.3613], and between day 0 and day 56 [Δ = 0.058 ± 0.340; P=0.7646]. Results are reported in Table 11.4, Table 11.5, and Table 14.1.1, Table 14.1.2, Table 14.1.3 and Listing 16.8.

There is no statistically significant difference comparing the two treatment periods, the intervention period (day 0-day 28) and the follow-up period (day 28-day 56) [Δ = -0.156 ± 0.325; P=0.1162)]. Details are reported in Table 11.6, and Table 14-5.

Table 11.3. Weekly Total Urea Kt/V, Single data at day 0, day 28 and day 56

Patient code	Group	Control visits		
		Day 0	Day 28	Day 56
1001-01	B	0,76	1,52	1,58
1001-02	B	1,59	1,75	1,56
1001-03	B	1,45	1,54	1,35
1001-04	A	1,24	1,08	1,14
1001-05	A	1,1	1,07	1,06
1001-06	A	1,68	1,7	1,49
1001-07	A	1,52	1,57	1,14
1001-08	B	1,36	1,47	1,35
1001-09	A	1,43	1,42	1,84
1001-11	A	1,12	1,42	1,49
1005-01	B	1,2	1,29	-
1005-02	B	1,23	1,12	1,12

Table 11.4. Weekly Total Urea Kt/V (Changes day 28 -day 0, treatment period)

	Day 0[a]	Day 28[b]	Changes (day 28 – day 0)
N	12	12	12
Mean	1.307	1.413	0.106
Standard deviation	0.253	0.230	0.239
Standard error	0.073	0.066	0.069
Median	0.760	1.445	0.070
Min - Max	1.300 - 1.680	1.070 – 1.750	-0.160-0.760
P*	⌊ ---------- 0.1694----------⌋		

[a] end of run-in period (with glucose PDS) (Visit 1); [b] end of treatment with investigational product (Visit 2)
*Wilcoxon Matched-Pairs Signed-Ranks test, changes day 28 – day 0

Table 11.5. Weekly Total Urea Kt/V (Changes day 56 -day 28, and day 56 - day 0)

	Day 0[a]	Day 28[b]	Day 56[c]
N	11	11	11
Mean	1.316	1.424	1.375
Standard deviation	0.263	0.238	0.244
Standard error	0.079	0.072	0.074
Median	1.360	1.470	1.350
Min - Max	0.760 – 1.680	1.070 – 1.750	1.060 – 1.840
P*		⌊----------0.3613**----------⌋	
	⌊ ----------0.7646----------⌋		

[a] end of run-in period (with glucose PDS) (Visit 1); [b] end of treatment with investigational product (Visit 2);
[c] end of follow-up period with glucose PD + icodextrin nightly (Visit 3)
* Wilcoxon Matched-Pairs Signed-Ranks test; ** Changes day 56-day 28, *** Changes day 56-day 0;

Table 11.6. Weekly Total Urea Kt/V - Comparison between periods (within patients)

	Intervention period (delta day 0 – 28)	Follow up period (delta day 28 – 56)	Changes Intervention vs follow-up
N	11	11	11
Mean	0.107	-0.049	-0.156
Standard deviation	0.251	0.219	0.325
Standard error	0.076	0.066	0.098
Median	0.050	-0.010	-0.230
Min - Max	-0.160 – 0.760	-0.430 – 0.420	-0.700 - 0.430
P*	-	-	0.1162

* Wilcoxon Matched-Pairs Signed-Ranks test

11.4.1.2 Peritoneal Equilibration Test (PET)

11.4.1.2.1 Peritoneal Equilibration Test (PET) – Dialysate/plasma creatinine

PET creatinine data for each patient at day 0 (end of run-in with glucose PDS), day 28 (end of treatment with the investigational product) and day 56 (end of follow-up period) are reported in Table 11-7.

Results show a statistically significant difference for the change in PET creatinine between day 0 (0.573 ± 0.130) and day 28 (0.643 ± 0.058), [Δ = 0.070 ± 0.148; P = 0.0322]. See Table 11.8.

There are no statistically significant differences for PET creatinine between day 28 and day 56 [Δ= -0.025 ± 0.057; P=0.2676] and between day 0 and day 56 [Δ= -0.051 ± 0.157; P=0.5156]. See Table 11.9.

Also, comparing the two treatment periods, there is a decrease in the PET creatinine values in the follow-up period (day 28 - day 56) compared to the intervention period (day 0 - day 28), which is statistically significant [Δ = -0.102 ± 0.170; P = 0.0225]. See Table 11.10.

Results are reported in Table 14.2.1, Table 14.2.2, Table 14.2.3, Table 14-6 and Listing 16.8.

Table 11.7. PET creatinine, Single data at day 0, day 28 and day 56

Patient code	Group	Control visits		
		Day 0	Day 28	Day 56
1001-01	B	0,66	0,74	0,7
1001-02	B	0,59	0,64	0,68
1001-03	B	0,61	0,67	0,7
1001-04	A	0,61	0,66	0,51
1001-05	A	0,22	0,72	0,7
1001-06	A	0,62	0,53	0,57
1001-07	A	0,57	0,6	0,62
1001-08	B	0,53	0,56	0,53
1001-09	A	0,57	0,59	0,57
1001-11	A	0,48	0,61	0,53
1005-01	B	0,71	0,71	-
1005-02	B	0,71	0,59	0,62

Table 11.8 PET creatinine - Changes day 28-day 0 (treatment period)

	Day 0[a]	Day 28[b]	Changes (day 28 – day 0)
N	12	12	12
Mean	0.573	0.643	0.070
Standard deviation	0.130	0.058	0.148
Standard error	0.037	0.017	0-043
Median	0.600	0.635	0.040
Min - Max	0.220-0.710	0.560-0.500	-0.120-0.500
P*		0.0322	

[a] end of run-in period (with glucose PDS) (Visit 1); [b] end of treatment with investigational product (Visit 2)
*Wilcoxon Matched-Pairs Signed-Ranks test, changes day 28 – day 0

Table 11.9. PET creatinine - Changes day 56 -day 28, and day 56-day 0

	Day 0[a]	Day 28[b]	Day 56[c]
N	11	11	11
Mean	0.561	0.637	0.612
Standard deviation	0.128	0.056	0.074
Standard error	0.039	0.017	0.022
Median	0.590	0.630	0.620
Min - Max	0.220 – 0.710	0.560 – 0.740	0.510 – 0.700
P*		⌊----------0.2676**---------- ⌋	
	⌊ ----------***0.5156----------⌋		

[a] end of run-in period (with glucose PDS) (Visit 1); [b] end of treatment with investigational product (Visit 2)
[c] end of follow-up period with glucose PD + icodextrin nightly (Visit 3)
* Wilcoxon Matched-Pairs Signed-Ranks test; ** Changes day 56-day 0; *** Changes day 56-day 28

Table 11.10. Peritoneal Equilibration Test (PET) creatinine: Comparison between periods.

	Intervention period (delta day 0 – 28)	Follow up period (delta day 28 – 56)	Changes Intervention vs Follow-up
N	11	11	11
Mean	0.076	-0.025	-0.102
Standard deviation	0.153	0.057	0.170
Standard error	0.046	0.017	0.051
Median	0.050	-0.020	-0.060
Min - Max	-0.120 – 0.500	-0.150 – 0.040	-0.520-0.150
P*	-	-	0.0225

* Wilcoxon Matched-Pairs Signed-Ranks test, change period 1 vs period 2

11.4.1.2.2 Peritoneal Equilibration Test (PET) glucose

PET glucose data for each patient at day 0 (end of run-in with glucose PDS), day 28 (end of treatment with the investigational product) and day 56 (end of follow-up period) are reported in Table 11-11.

For PET glucose, there are no statistically significant differences between day 0 and day 28 [Δ=0.037± 0.103; P=0.2695], between day 28 and day 56 [Δ= 0.013±0.69; P=0.6563], day 0 and day 56 [Δ=0.050±0.089; P= 0.0547]. See Table 11.12, Table 11.13, Table 11.14.

Table 11.11.Peritoneal Equilibration Test (PET) glucose, Single data at day 0, day 28 and day 56

Patient code	Group	Control visits		
		Day 0	Day 28	Day 56
1001-01	B	0,18	0,23	0,23
1001-02	B	0,29	0,34	0,26
1001-03	B	0,27	0,3	0,24
1001-04	A	0,31	0,28	0,37
1001-05	A	0,24	0,22	0,22
1001-06	A	0,27	0,27	0,31
1001-07	A	0,32	0,27	0,42
1001-08	B	0,34	0,32	0,34
1001-09	A	0,23	0,28	0,29
1001-11	A	0	0,31	0,27
1005-01	B	-	-	-
1005-02	B	-	-	-

Table 11.12 PET glucose - Changes day 28 -day 0 (treatment period)

	Day 0[a]	Day 28[b]
N	10	10
Mean	0.245	0.282
Standard deviation	0.098	0.038
Standard error	0.031	0.012
Median	0.270	0.280
Min - Max	0 – 0.340	0.220 – 0.340
P*	0.2695	

[a] end of run-in period (with glucose PDS) (Visit 1); [b] end of treatment with investigational product (Visit 2);
* Wilcoxon Matched-Pairs Signed-Ranks test, changes day 28-day 0

Table 11.13. PET glucose - Changes day 56 -day 28, and day 56-day 0

	Day 0[a]	Day 28[b]	Day 56[c]
N	10	10	10
Mean	0.245	0.282	0.295
Standard deviation	0.098	0.038	0.065
Standard error	0.031	0.012	0.021
Median	0.270	0.280	0.280
Min - Max	0 – 0.340	0.220 – 0-340	0.220 – 0.420
P*		⌊----------0.6563**---------- ⌋	
	⌊ ----------***0.0547----------⌋		

[a] end of run-in period (with glucose PDS) (Visit 1); [b] end of treatment with investigational product (Visit 2);
[c] end of follow-up period with glucose PD + icodextrin nightly (Visit 3)
* Wilcoxon Matched-Pairs Signed-Ranks test; ** Changes day 56-day 0; *** Changes day 56-day 28

Table 11.14. Peritoneal Equilibration Test (PET) glucose: Comparison between periods.

	Intervention period (delta day 0-28)	Follow up period (delta day 28-56)	Changes Intervention vs Follow-up
N	10	10	10
Mean	0.037	0.013	-0.024
Standard deviation	0.103	0.069	0.150
Standard error	0.032	0.022	0.048
Median	0.015	0.005	-0.010
Min - Max	-0.050-0.310	-0.080-0.150	-0.350-0.200
P*	-	-	0.7129

* Wilcoxon Matched-Pairs Signed-Ranks test

11.4.1.3. Weekly Total Creatinine Clearance

Creatinine Clearance data for each patient at day 0 (end of run-in with glucose PDS), day 28 (end of treatment with the investigational product) and day 56 (end of follow-up period) are reported in Table 11.15.

There are no statistically significant differences between day 0 and day 28 [Δ=2.71 ± 12.09; P= 0.3394], and between day 28 and day 56 [Δ= -4.25 ± 11.42; P= 0.5195], day 0 and day 56 [Δ= -1.11 ± 13.17; P= 0.5771]. Comparing the two periods, the follow-up period and the intervention period, there is no statistically significant difference [Δ= -10.92 ± 22.75; P= 0.46].
Results are reported in Table 11.16, Table 11.17, Table 11.18, Table 14.3.1, Table 14.3.2, Table 14.3.3, Table 14-7 and Listing 16.8.

Table 11.15. Weekly Total Creatinine Clearance, Single data at day 0, day 28 and day 56

Patient code	Group	Control visits		
		Day 0	Day 28	Day 56
1001-01	B	61,46	69,88	70,98
1001-02	B	86,94	98,15	80,7
1001-03	B	72,22	65,83	68,22
1001-04	A	50,03	42,38	42,6
1001-05	A	78,04	55,45	59,66
1001-06	A	93,39	105,74	91,53
1001-07	A	77,76	79,55	58,06
1001-08	B	62,62	65,56	62,31
1001-09	A	85,52	95,78	112,38
1001-11	A	55,46	80,25	65,26
1005-01	B	53,87	51,85	-
1005-02	B	43,28	42,69	42,83

Table 11.16 Weekly Total Creatinine Clearance – Changes day 28- day 0 (treatment period)

	Day 0[a]	Day 28[b]	Changes (day 28-day 0)
N	12	12	12
Mean	63.38	71.09	2.71
Standard deviation	16.20	21.33	12.09
Standard error	4.68	6.16	3.49
Median	67.42	67.85	2.36
Min - Max	43.28-93.39	42.38-105.74	-22.59 – 24.79
P*		0.3394	

[a] end of run-in period (with glucose PDS) (Visit 1); [b] end of treatment with investigational product (Visit 2)
* Wilcoxon Matched-Pairs Signed-Ranks test, changes day 28-day 0

Table 11.17. Weekly Total Creatinine Clearance - Changes day 56 -day 28, and day 56-day 0

	Day 0[a]	Day 28[b]	Day 56[c]
N	11	11	11
Mean	69.70	72.84	68.59
Standard deviation	16.30	21.45	20.44
Standard error	4.91	6.47	6.16
Median	72.22	69.88	65.26
Min - Max	43.28-93.39	42.38-105.74	42.60-112.38
P*		|----------0.5195**---------- |	
	|----------0.5771***----------|		

[a] end of run-in period (with glucose PDS) (Visit 1); [b] end of treatment with investigational product (Visit 2)
[c] end of follow-up period with glucose PD + icodextrin nightly (Visit 3)
* Wilcoxon Matched-Pairs Signed-Ranks test; ** Changes day 56-day 28; *** Changes day 56-day 0

Table 11.18 Changes in Weekly Total Creatinine Clearance: Comparison between periods

	Intervention period (Δ day 0-28)	Follow-up period (Δ day 28-56)	Changes Intervention vs Follow-up
	11	11	11
Mean	3.14	-4.25	-7.39
Standard deviation	12.58	11.42	20.10
Standard error	3.79	3.44	6.06
Median	2.94	0.14	-6.19
Min - Max	-22.59-24.79	-21.49-16.60	-39.78-26.80
P*		0.4648	

* Wilcoxon Matched-Pairs Signed-Ranks test

11.4.1.4. Total Ultrafiltration

Ultrafiltration data for each patient at day 0 (end of run-in with glucose PDS), day 28 (end of treatment with the investigational product) and day 56 (end of follow-up period) are reported in Table 11.19.

There is no statistically significant difference comparing day 0 and day 28 [Δ= 37.50 ± 128.14; P= 0.5000]. However, there is a statistically significant difference between day 28 (354.17 ± 264.11) and day 56 (483.33 ± 289.46) [Δ= 129.17±143.75; P = 0.0117], and between day 0 (316.67 ± 271.64) and day 56 (483.33 ± 289.46) [Δ= 167.67±154.23; P=0.0039). There is no statistically significant difference between the two treatment periods [Δ= 91.67 ± 224.45; P=0.24].

Results are reported in Table 11.20, Table 11.21, Table 14.4.1, Table 14.4.2, Table 14.4.3, Table 14-8 and Listing 16.4.

Table 11.19. Total Ultrafiltration, Single data at day 0, day 28 and day 56

Patient code	Group	Control visits				
		Day 0	Day 14	Day 28	Day 42	Day 56
1001-01	B	400	300	300	300	450
1001-02	B	400	400	400	500	400
1001-03	B	300	300	300	300	300
1001-04	A	0	100	200	200	400
1001-05	A	0	100	100	0	0
1001-06	A	100	250	100	300	300
1001-07	A	300	200	200	900	600
1001-08	B	300	300	300	600	600
1001-09	A	300	300	300	400	500
1001-11	A	250	300	300	250	300
1005-01	B	400	700	750	1050	800
1005-02	B	1050	1050	1000	1500	1150

Table 11.20 Total Ultrafiltration – Changes day 28-day 0, day 56-day 28, and day 56-day 0

	Day 0[a]	Day 28[b]	Day 56[c]
	12	12	12
Mean	316.17	354.17	483.33
Standard deviation	271.64	263.11	289.46
Standard error	78.42	76.24	83.56
Median	300	300	425.00
Min – Max	0.0-1050	100-1000	0.0-1150.0
P*	⌊ ----------*0.5000----------⌋		
		⌊----------0.0117**---------- ⌋	
	⌊----------0.0039***----------⌋		

[a] end of run-in period (with glucose PDS) (Visit 1); [b] end of treatment with investigational product (Visit 2)
[c] end of follow-up period with glucose PD + icodextrin nightly (Visit 3);
* Wilcoxon Matched-Pairs Signed-Ranks test; * Changes day28-day0; ** Changes day56-day28; *** Changes day56-day0

Table 11.21 Changes in Total Ultrafiltration: Comparison between periods

	Intervention period (Δ day 0 – 28)	Follow up period (Δ day 28 – 56)	Changes Intervention vs follow-up
N	12	12	12
Mean	37.50	129.17	91.67
Standard deviation	128.14	143.75	224.45
Standard error	36.99	41.50	64.79
Median	0	150.0	100.0
Min - Max	-100.0-350.0	-100.0-400.0	-300.0-500.0
P*	-	-	0.2422

* Wilcoxon Matched-Pairs Signed-Ranks test;

11.4.2 Statistical/Analytical Issues

11.4.2.1. Interim Analyses and Data Monitoring

The protocol did not include a formal interim analysis.

11.4.2.2 Handling of Dropouts or Missing Data

Study protocol stated that no particular approach for missing data were applied.

1.4.2.3 Multicenter Studies

For all primary and secondary efficacy analyses, data were combined from all recruiting centers and summarised for all subjects.

11.4.4 Tabulation of Individual Response Data

Individual data on Weekly Total Urea Kt/v, Peritoneal Equilibration Test (PET) and Weekly total Creatinine Clearance are presented in Listing 16.8. Ultrafiltration data are presented in Listing 16.4.

11.4.5 Study Drug Dose, Concentration, and Dose-Response Relationships

Samples for determination of free carnitine and its acyl-derivatives levels in blood, urine, and peritoneal effluent were obtained from all 12 patients.

For all patients, in the last day of the Screening Period (day 0), a venous blood sample (5 mL) was drawn in the morning, after nocturnal dwell, concomitantly with a peritoneal effluent sample (10mL) and a urine sample (10mL) from the 24-hour urine collection, for the assessment of basal levels of total carnitine (TC), free carnitine (FC) and acetyl-carnitine (AC).

Additional blood samples (5 mL) were taken on days 14, 28, 42, and 56 at the end of the nocturnal dwell after the peritoneum was emptied. Dialysate samples (10 mL) were collected from the effluent obtained after nocturnal dwell on days 14, 28, 42, and 56. The urine samples (10 mL) were collected on day 14, 28, 42, 56 from the 24-hour urine collected during the day before the hospital visit.

Table 11.22 shows mean (SD) serum, urinary and dialysate L-Carnitine and Acetyl-L-Carnitine

Figure 11.1 shows graphically the profile of the curves of serum L-carnitine values of each patient, over time.
Figure 11.2 shows the serum L-carnitine levels per group over time. Please note that patients of Group A received one solution bag of investigational product (IXP15 containing carnitine 0.02%) during the nocturnal exchange. Patients of Group B received 2 solution bags (IXP07, containing L-carnitine 0.02%) during the diurnal exchanges, apart from patient 01-002, who received only one bag (only one diurnal exchange).
Figure 11.3 shows the profile of the curves of urine L-carnitine in each patient over time.
Figure 11.4 show the urine L-carnitine levels per group over time.
Figure 11.5 shows the profile of the curves of serum acetyl-L-carnitine in each patient, over time.
Figure 11.6 shows the profile of urine acetyl-L-carnitine levels in each patient over time.

Individual data on free carnitine (L-carnitine) and its acyl-derivatives (acetyl-L-carnitine) plasma levels are presented in Listing 16.14.1-2, urine levels in Listing 16.15.1-2 and peritoneal effluent (dialysate) in Listing 16.16.1-2.

Table 11.22. Mean (SD) serum, urinary and dialysate L-Carnitine and Acetyl-L-Carnitine

	Day 0	Day 14	Day 28	Day 42	Day 56
Serum L-carnitin	51,08±23.31	139.08±46.88	149.41±38.80	66.5±12.41	59±11
Serum Acetyl-L-carnitine	9.58±4.21	35.16±18.39	34.66±17.41	12±4.49	10.16±3.10
Urine L-carnitine	45.33±45.25	322.77±191.48	255.26±122.57	43.26±32.87	35.94±15.74
Urine Acetyl-L-carnitine	16.07±21.49	134.74±43,68	102.14±41.33	14.61±8.78	17.14±15.46
Dialysate L-carnitine	38.74±20.83	272.58±174.54	142.91±71.87	51.5±11.47	48.39±7.72
Dialysate Acetyl-L-carnitine	7.05±4.18	26.84±18.49	30.68±15.97	9.06±4.42	8.11±2.78

Results are expressed in µmol/l

Figure 11.1. Overlay of serum L-carnitine levels by patients

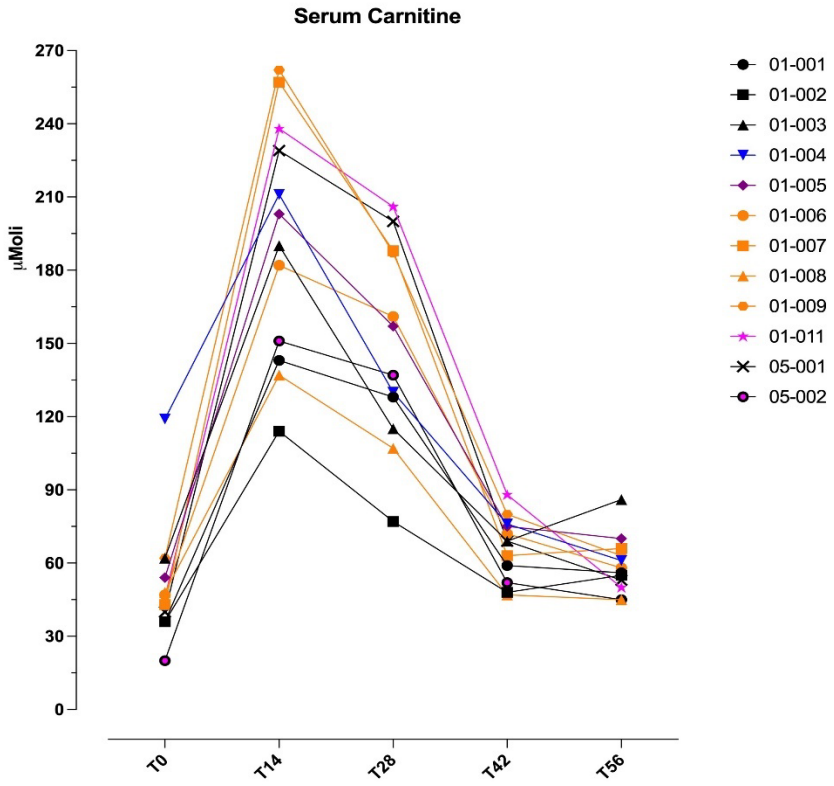


Figure 11.2 Serum L-carnitine by treatment group

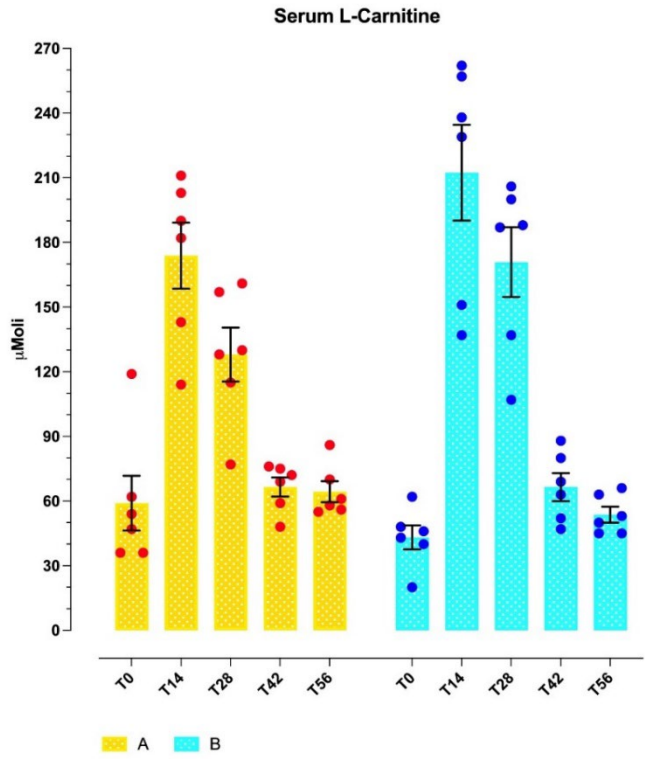


Figure 11.3 Overlay of urine L-carnitine levels by patients

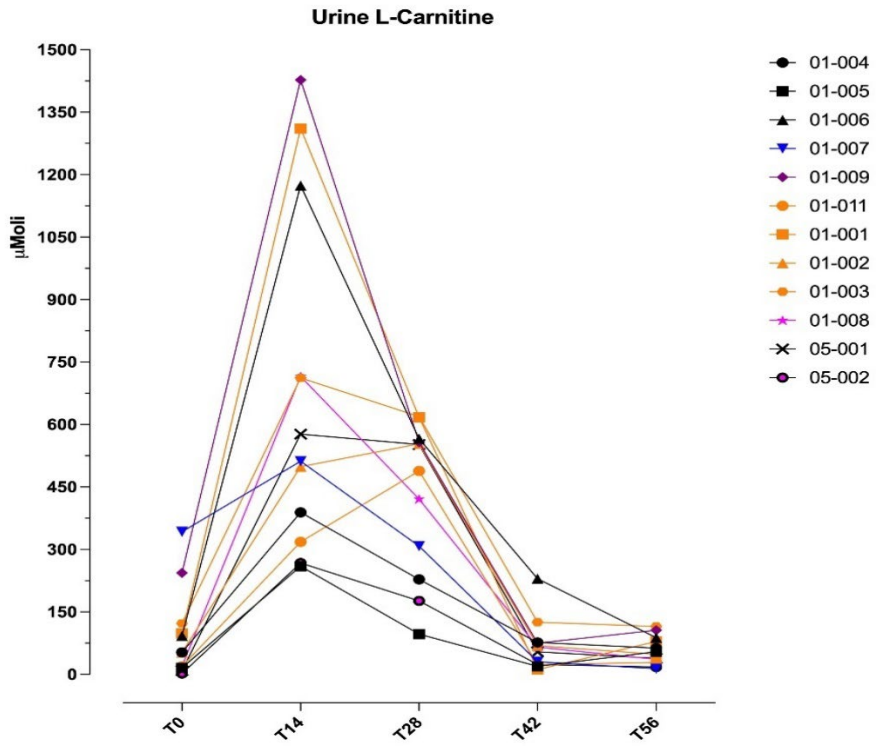


Figure 11.4 Urine L-carnitine by treatment group

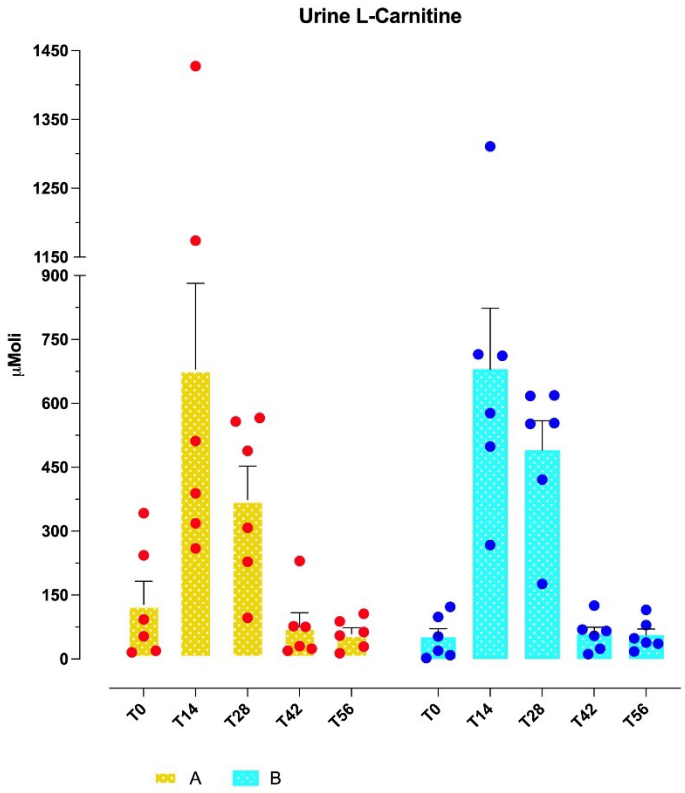


Figure 11.5 Overlay of serum Acetyl L-carnitine levels by patients

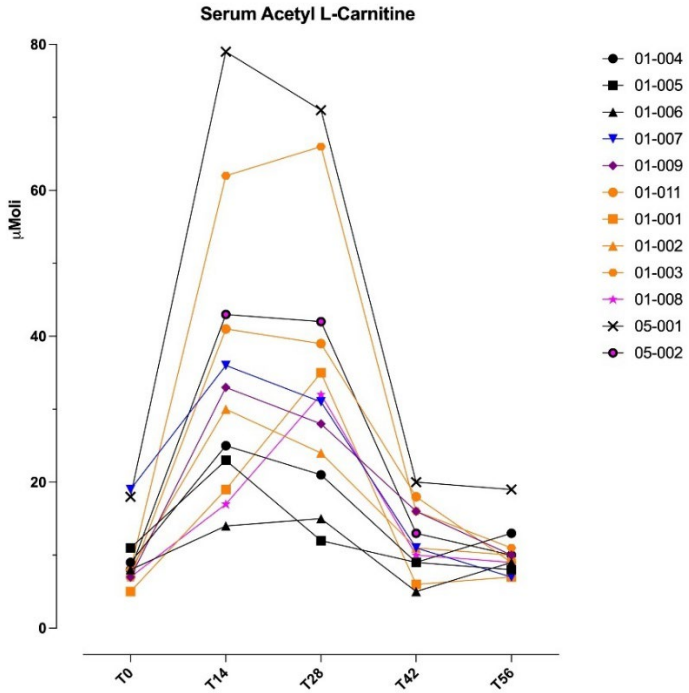
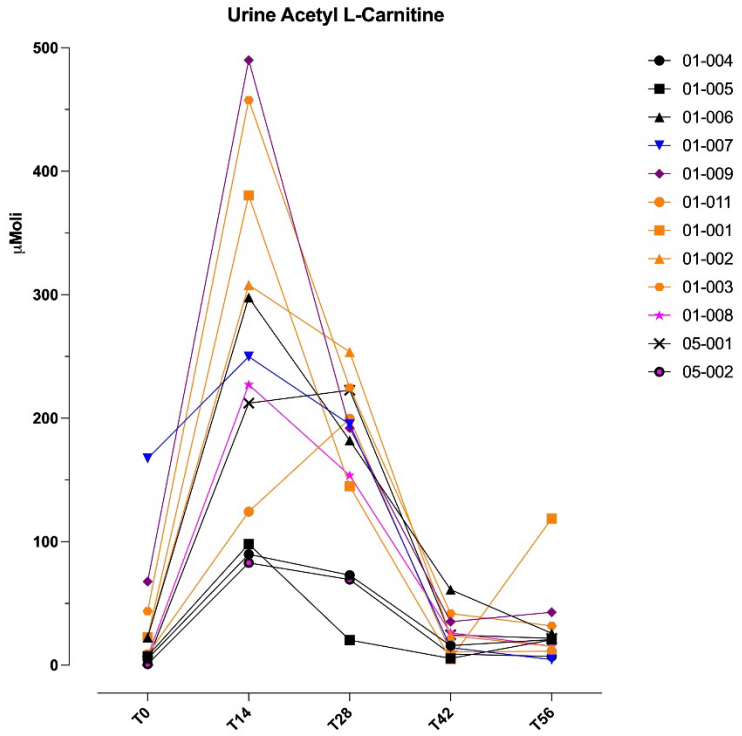


Figure 11.6 Overlay of urine Acetyl L-carnitine levels by patients



11.4.6 Drug-Drug and Drug-Disease Interactions

Listing 16.12 provides a list of all previous and concomitant medications per subject.

11.4.6 By-Subject Displays

Not applicable.

11.4.8 Efficacy Conclusion

The study had a premature conclusion due to difficulties in enrolling patients. Of the 80 patients planned, 13 patients have been enrolled and 12 completed the study.

No statistically significant differences have been seen between the treatment period with the investigational product (days 0 to 28) and the follow up period with glucose + icodextrin nightly (days 28 to 56) for weekly Kt/V and weekly Total Creatinine Clearance.

Evaluation of peritoneal membrane characteristics by Peritoneal Equilibration Test (PET) showed that patients were average transporters. Results show an increase in the PET creatinine comparing day 28 with day 0, which was statistically significant (P=0.0322 with Wilcoxon Matched-Pairs Signed-Rank test). A direct comparison between periods (changes during the follow-up period compared with changes in the treatment period) showed a decrease in PET creatinine during follow up, which was statistically significant (P= 0.0225). No statistically significant difference in PET glucose has been seen between day 0 and day 28, between day 28 and day 56, and day 0-day 56.

The peritoneal equilibration test (PET) is used to evaluate peritoneal membrane characteristics and individualize PD prescriptions. An increase in membrane permeability, expressed as increase of PET creatinine and decrease PET glucose is generally expected during long-term peritoneal dialysis, in particular for patients developing ultrafiltration failure (91). Ideally, an optimal solution for peritoneal dialysis should optimize small solutes transport (PET creatinine) while maintaining PET glucose as higher as possible. Interestingly, in this study, while PET creatinine slightly increased during the treatment and decreased during follow-up, PET glucose remained stable over the study (increased without a statistical significance). If these data will be confirmed, it might be speculated that the IMP improves the peritoneal clearance of small solutes (creatinine) without an increase in glucose absorption, and a consequent osmolar gradient dissipation, as expected by Twardowsky graph (92) and clinical experience.

For Total Ultrafiltration, a statistically significant difference has been seen comparing day 28 and day 56 (end of the follow up with glucose + icodextrin nightly) (P= 0.0117). Also, the difference between day 56 and day 0 was statistically significant (P= 0.0039). However, a comparison between periods (changes during the follow-up period compared with changes in the treatment period) was not significant. Also, it should be noted that daily water removal (sum of peritoneal ultrafiltration and diuresis) was maintained during the study day 0 (1.938 ± 0.62), day 28 (1.996 ± 0.50) day 56 (2.092 ± 0.46), with no statistically significant changes, suggesting the IMP should be as effective as commercially available glucose-based PD solutions. Ultrafiltration showed a positive trend during the whole study, suggesting a potential carry-over effect. Considering the intrinsic variability of ultrafiltration data, this study is clearly insufficient to draw any conclusion and further investigations are needed.

The determination of L-carnitine in serum, urine, and dialysate show profiles between days 0, 14, 28, 42 and 56, representing an increase of concentration during the treatment period (day 0 to 28), which reduced up to day 42 returning to values similar to the baseline by day 56.

12 SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

The intervention period lasted 4 weeks. The subjects included in the Group A received a bag with experimental solution (IXP15) for the nocturnal dwell, and the subjects included in the Group B received 1, 2 or 3 bags with the experimental solution (IXP07) for the daily exchanges and a bag with icodextrin solution for the nocturnal dwell.

A total of 13 patients received investigational product. Seven patients (Group A) received 1 bag of IXP15 for nocturnal CAPD exchange, and 6 other patients received IXP07 for 1, 2, 3 diurnal exchanges (5 patients received 2 exchanges and 1 patient received 1 exchange). One patient (Subject 01-010 in Group A was lost to follow up before day 28 visit and received 14 bags of investigational product, only).

Table 12-1 reports the exposure during the study. Please also refer to Listing 16.13.

Table 12-1. Exposure to the Investigational product (treatment phase, day 28 to day 56)

	INVESTIGATIONAL TREATMENT IXP15 (GROUP A)	INVESTIGATIONAL TREATMENT IXP07 (GROUP B)	OVERALL. INVESTIGATIONAL PRODUCT
Subjects who received investigational product	7*	6	13
Bags used by patients			
• Number of bags	180	300	480
• Mean	25.71	46.57	36.92
• Standard deviation	4.82	12.6	14.37
• Median	28	55	28
• Min - Max	26 - 28	28-56	26-56

* Subject 01-010 lost to follow up before day 28 visit (during run-in: the subject did not receive treatment)

12.2 ADVERSE EVENTS

12.2.1 Brief Summary of Adverse Events

Overall, 9 AEs by 5 subjects (38.46%) were reported during the treatment phase. Four subjects were in study Group B and 1 subject in Group B.

An overview of adverse events during the treatment phase is presented in Table 12-2. Please refer to Listing 16.11.

There were no Serious Adverse Events. No adverse events lead to discontinuation of study medication or death.

Table 12-2. Overview of Adverse Events

Safety Analysis Population	N=12
Subjects with Any AE (incl. SAE)	5 (38.46%)
Number of AEs (incl. SAEs)	9
Subjects with Any SAE	-
Subjects with Any drug related AE	-
Subjects with Any AE leading to death	-
Subjects with Any AE leading to discontinuation	-

12.2.2 Display of Adverse Events

12.2.2.1 Incidence of All Treatment Emergent Adverse Events

Adverse Events were summarised by system organ class (SOC) and preferred term (PT) using MedDRA version 23.1. Only 1 AE was in Group A patients (Subject 01-004, received IXP15 and had hyperphosphatemia which was mild in intensity and considered not related).

Overall, 9 AEs by 5 subjects (38.6%) were reported during treatment phase. No adverse event led to the discontinuation of the study medication, death, or were considered related to investigational product,

The AE are reported in Table 12-3 and Listing 16.11.

Table 12-3. Summary of Adverse Events by MedDRA SOC and PT

Adverse Events	Number of AEs
Anemia	1
Turbid peritoneal fluid	1
Hyperphosphataemia	1
Macroglossia	1
Insomnia	1
Dispnea	1
Itching	1
Swollen legs	1
Mild bilateral legs edema	1

12.2.2.2 Incidence of Drug-related Adverse Events

In this study there was no drug-related adverse events. Drug-related adverse events were those considered to be possibly, probably or definitely related to study treatment by the Investigator.

12.2.2.3 Discontinuation Due to Adverse Events

No adverse event led to the discontinuation of the study medication.

12.2.3 Analysis of Adverse Events

The mean number of exposures to Investigational therapy for peritoneal dialysis during the treatment period (28 days) was 480 exposures. At the time of database freezing for the statistical analysis, 12 patients completed the study.

Overall, 9 AEs by 5 subjects (38.46%) were reported during the treatment phase. A summary of Adverse Events by MedDRA Preferred Term is reported in Table 12-3 and Listing 16-13.

No adverse event led to the discontinuation of the study medication, death, or considered related to the treatment. There were no Serious Adverse Events.

12.2.4 Listing of Adverse Events by Patient

Adverse Events for individual patients are provided in Listing 16.11.

12.3 Death, Other Serious Adverse Events, and Other Significant Adverse Events

No death was reported during the study. There were no Serious Adverse Events.

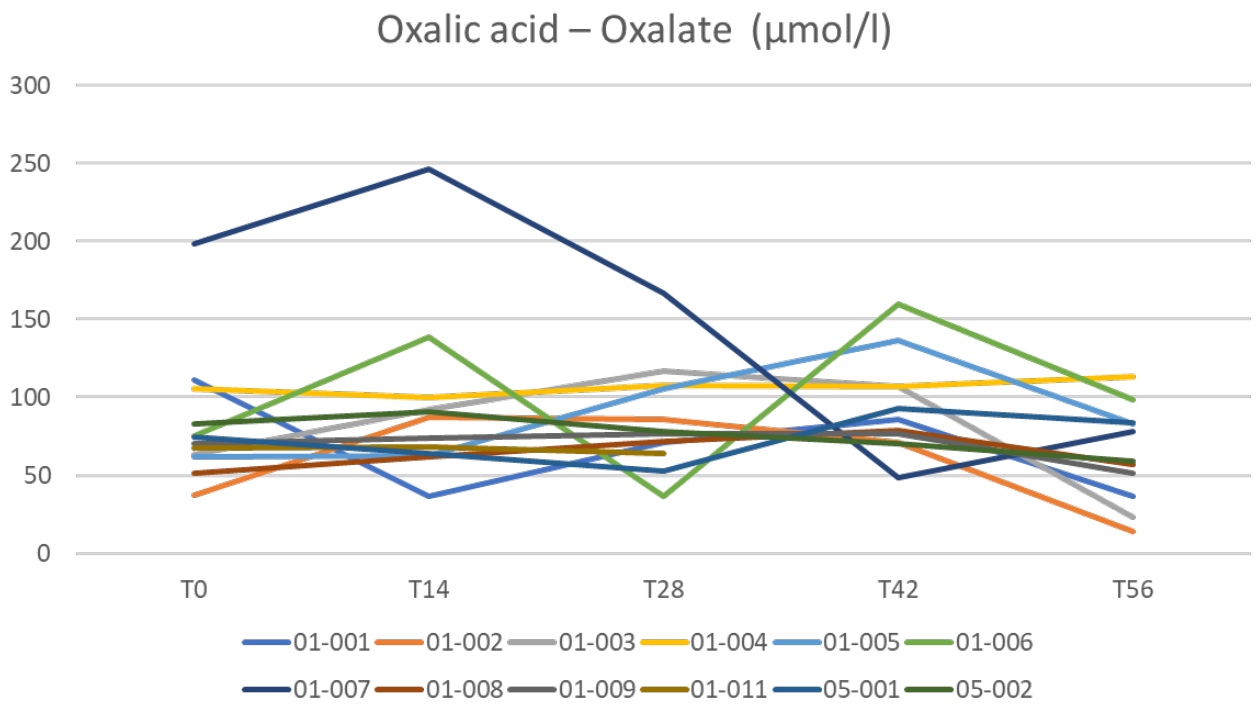
12.4 Clinical Laboratory Evaluation

12.4.1 Laboratory results

Haematology [hemoglobin, hematocrit, RBC count, WBC count and WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count]: All parameters were assessed as "Normal" or "Not Clinically Significant" between Day 0 and Day 56

Biochemistry [serum sodium, potassium, calcium, phosphorus, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, fasting glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol triglycerides, blood urea nitrogen (BUN), creatinine]: All parameters were assessed as "Normal" or "Not Clinically Significant" between Day 0 and Day 56. Uric and lactic acids were assessed as "Normal" or "Not Clinically Significant" between Day 0 and Day 56. Oxalic acid results are presented in Figure 12.1 and Listing 16.17.

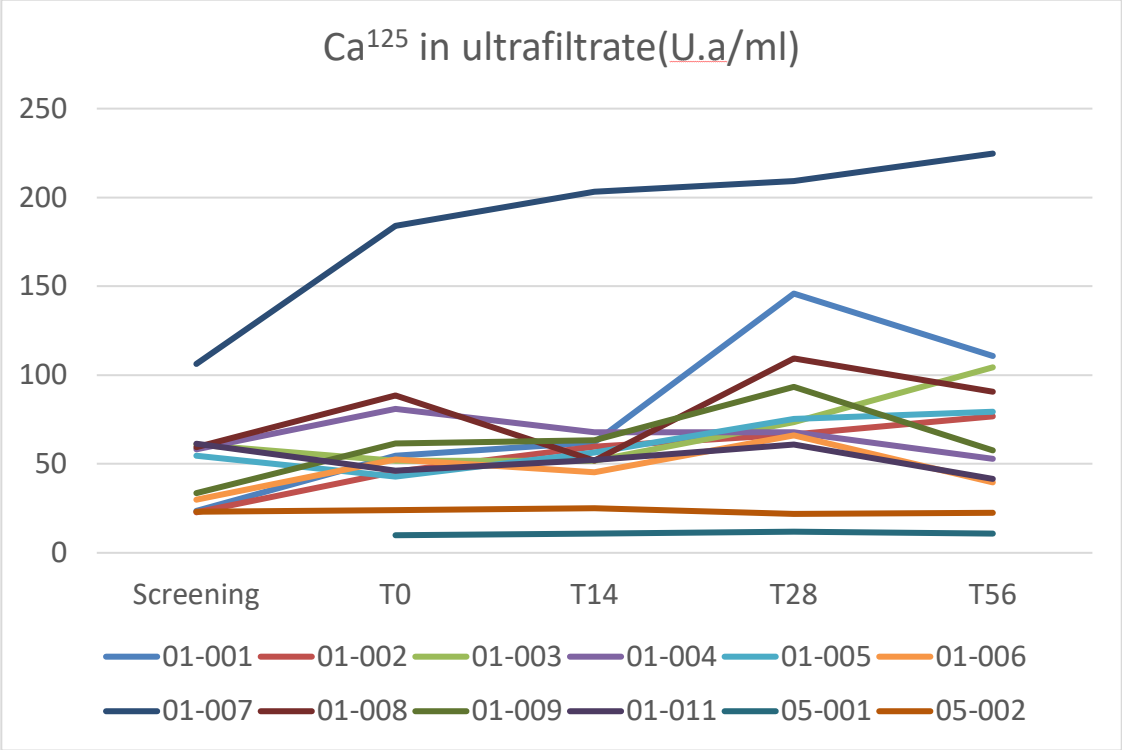
Figure 12.1. Overlay of oxalic acid levels curves by patient



Ca^{125} in the ultrafiltrate

CA^{125} in the ultrafiltrate (effluent), a glycoprotein with high molecular weight, is considered as a marker of the mesothelial cells mass. In dialysis patients, CA^{125} is normal, but the high concentration in peritoneal effluent suggests a local release of mesothelial cells. A decrease of CA^{125} level in peritoneal effluent over time indicates the loss of mesothelial cells, thus CA^{125} being a in vivo marker of peritoneal solution biocompatibility. Ca^{125} in ultrafiltrate results are presented in Figure 12.2 and Listing 16.4.

Figure 12.2. Overlay of Ca^{125} levels in ultrafiltrate curves by patient



Proteins in the ultrafiltrate

The loss of proteins in the ultrafiltrate (peritoneal effluent) will be used as marker of the experimental solution tolerability.

Results show that proteins in the ultrafiltrate quite stable between patients and do not reduce over time. Individual patient data are presented in Listing 16.4.

12.4.2 Listing of individual laboratory measurements by patient

Please refer to Listings 16.6.1-10 (Haematology), Listing 16.7.1-18 (Biochemistry), Listing 16.5 (Uric and lactic acids), Listing 16.17 (Oxalic acid), Listing 16.4 (Ca^{125} and proteins in ultrafiltrate)

12.4.3 Evaluation of each laboratory parameter

In all patients, haematology and biochemistry parameters, including uric and lactic acids, were assessed as “Normal” or “Not Clinically Significant” between Day 0 and Day 56.

As expected, all patients had higher than normal values of creatinine and BUN, starting from the screening visit, which were considered “Not Clinically Significant”. In Subject 01-003, starting from the screening visit, they were considered “Clinically significant for concomitant disease”, and Subject 01-011 “Clinically significant for the pathology under the study” even if the creatinine and BUN levels were similar to the other patients.”

All patients had lower than normal values of hemoglobin starting from the screening visit, which the Investigators considered "Not Clinically Significant". However, in Subject 01-001, starting from the screening visit, they were considered "Clinically significant for concomitant disease", and in Subject 01-011, "Clinically significant for the pathology under the study", even if the hemoglobin levels were similar to the other patients.

Oxalic acid levels by patient are reported in the Figure 12.1.

12.5 VITAL SIGNS, PHYSICAL FINDING, AND OTHER OBSERVATIONS RELATED TO SAFETY

Physical examination, clinical parameters, including weight, arterial blood pressure, heart rate, diuresis (L/day) and hyperhydration signs, as well as a 12-lead electrocardiogram (ECG) determinations were performed by the investigator at the site (local dialysis center) during the screening period (day -28) day 0, during the intervention period (day 14 and 28), and during the follow up period (day 42 and 56). All clinical parameters have been assessed by Investigators "Normal" or "Not clinically significant".

For ECG, some patients had clinically significant alterations due to concomitant diseases (patient 01-001. 01-005, 01-006 had sinus bradycardia at day 0 and day 28; patient 01-007 had left bundle branch block at day 0 and 28; patient 01-009 had sinus rhythm alteration and previous lower myocardial infarction).

Listing of physical examinations are provided in Listing(s) 16.2.3, clinical parameters in Listing 16.3, ECG in Listing 16.10.

12.6 SAFETY CONCLUSIONS

Data on 13 completed patients were available at the time of freezing of the database the statistical analysis. There were 480 single administrations of the investigational product for peritoneal dialysis.

Overall, 9 AEs by 5 subjects (38.46%) were reported. A summary of Adverse Events is reported in Table 12.3 and Listing 16.11. No adverse event led to the discontinuation of the study medication, death, or was considered related to the investigational product. All AEs were mild or moderate in intensity. There were no Serious Adverse Events.

Vital signs, clinical examinations, and electrocardiographic findings did not raise safety concerns. No patient showed serious signs of overhydration or had appreciable changes in body weight during the study. Haematology and Biochemical parameters showed no clinically significant changes at the different time points during the study.

CA^{125} is a glycoprotein with high molecular weight considered as a marker of the mesothelial cells mass. In peritoneal dialysis patients, CA125 in dialysate is normal, but a high concentration in peritoneal effluent suggests a local release of mesothelial cells. A decrease of CA125 level in peritoneal effluent over time indicates the loss of mesothelial cells, thus CA125 being a in vivo marker of peritoneal solution biocompatibility. Similarly, the loss of proteins in the ultrafiltrate (peritoneal effluent) is used as marker of the experimental solution tolerability. Results show that CA^{125} and proteins in the ultrafiltrate quite stable between patients and do not reduce over time.

13 DISCUSSION AND OVERALL CONCLUSIONS

The study had a premature conclusion due to difficulties in enrolling patients. Of the 80 patients planned, 13 patients have been enrolled, and 12 completed the study.
During the four-week study period, patients included in group A received a bag with the experimental solution IPX15 for the nocturnal dwell; group B subjects received one or two bags with the experimental solution IPX07 for the daytime exchanges and a bag with icodextrin solution for the nocturnal dwell.
There were 480 single administrations of the investigational product for peritoneal dialysis.
Data on 13 enrolled patients, with 12 completed the study, were available at the time of freezing of the database for the statistical analysis.
Tolerability was good. Overall, 9 AEs by five subjects (38.46%) were reported. A summary of Adverse Events is reported in Table 12.3 and Listing 16.11. No adverse event led to the discontinuation of the study medication, death, or was considered related to the investigational product. All AEs were mild or moderate in intensity. There were no Serious Adverse Events.
Vital signs, clinical examinations, and electrocardiographic findings did not raise safety concerns. No patient showed severe signs of overhydration or had appreciable changes in body weight during the study. Haematology and Biochemical parameters, including uric and lactic acids, showed no clinically significant changes at the different time points of the study. Oxalic acid levels did not change during the study.
CA^{125} is a glycoprotein with high molecular weight considered a marker of the mesothelial cell mass. In peritoneal dialysis patients, CA^{125} in the dialysate is normal, but a high concentration in peritoneal effluent suggests a local release of mesothelial cells. A decrease of CA^{125} level in peritoneal effluent over time indicates the loss of mesothelial cells. Thus, CA is an in vivo marker of peritoneal solution biocompatibility. Similarly, the loss of proteins in the ultrafiltrate (peritoneal effluent) will is used as marker of the experimental solution tolerability. Results show that CA^{125} and proteins in the ultrafiltrate are stable between patients and do not reduce over time.

Regarding efficacy, no statistically significant differences have been seen between the treatment period with the investigational product (days 0 to 28) and the follow up period with glucose (days 28 to 56) for weekly Kt/V and weekly Total Creatinine Clearance.

Evaluation of peritoneal membrane characteristics by Peritoneal Equilibration Test (PET) showed that patients were average transporters. Results show an increase in the PET creatinine comparing day 28 with day 0, which was statistically significant (P=0.0322 with Wilcoxon Matched-Pairs Signed-Rank test). A direct comparison between periods (changes during the follow-up period compared with changes in the treatment period) showed a decrease in PET creatinine during follow up, which was statistically significant (P= 0.0225). No statistically significant difference in PET glucose has been seen between day 0 and day 28, between day 28 and day 56, and day 0-day 56.

The peritoneal equilibration test is used to evaluate peritoneal membrane characteristics and individualize PD prescriptions. An increase in membrane permeability, expressed as increase of PET creatinine and decrease of PET glucose is generally expected during long-term peritoneal dialysis, in particular for patients developing ultrafiltration failure (91). Ideally, an optimal solution for peritoneal dialysis should optimize small solutes transport (PET creatinine) while maintaining PET glucose as higher as possible.

Interestingly, in this study, while PET creatinine slightly increased during the treatment and decreased during follow-up, PET glucose remained stable over the study (increased without a statistical significance). If these data will be confirmed, it might be speculated that the IMP improves the peritoneal clearance of small solutes (creatinine) without an increase in glucose absorption, and a consequent osmolar gradient dissipation, as expected by Twardowsky graph (92) and clinical experience.

For Total Ultrafiltration, a statistically significant difference has been seen comparing day 28 (end of the treatment period with the IMP) and day 56 (end of the follow up with glucose + icodextrin nightly) (P= 0.0117). Also, the difference between day 56 and day 0 was statistically significant (P= 0.0039). However, a comparison between periods (changes during the follow-up period compared with changes in the treatment period) was not significant. Ultrafiltration showed a positive trend during the whole study, suggesting a potential carry-over effect. Considering the intrinsic variability of ultrafiltration data, this study is clearly insufficient to draw any conclusion and further investigations are needed.

The determination of L-carnitine in serum, urine and dialysate show profiles between days 0, 14, 28, 42, and 56 representing an increase of concentration during the treatment period (day 0 to 28), which reduced up to day 42, returning to values similar to the baseline by day 56. Urine and dialysate concentrations correspond to the changes seen in the blood.

Six patients in group A and six in group B completed study treatments. Due to the incomplete sample size enrolled (12 patients of the 80 planned), data from the two treatment groups (A and B) have been pooled to increase the informative value of the study.
The primary study objectives were to evaluate the safety and tolerability of the experimental solutions. The secondary objectives were to assess the performance of the peritoneal dialysis with the investigational product, specifically the peritoneal clearances and peritoneal transport characteristics for Day 0 and the follow-up period, to evaluate if the investigational product allows for an adequate peritoneal dialysis, which should be at least non-inferior of glucose solutions. The tests used in the study (Kt/v, PET, Creatinine clearance, and Ultrafiltration) show the effects of the PD product on peritoneal dialysis performance.

Taken together, safety and efficacy data suggest the investigational product is well tolerated and should be as effective as commercially available glucose-based PD solution. A confirmatory study is needed to demonstrate its non-inferiority compared with commercial glucose-based PD solutions.

14 TABLES

Table 1.1: Weekly Total Urea Kt/V - Changes (day 28-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	12	1.307	0.253	0.073	0.760	1.300	1.680
Visit 2 (day 28)	12	1.413	0.230	0.066	1.070	1.445	1.750
Changes (day 28-day 0)	12	0.106	0.239	0.069	-0.160	0.070	0.760

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.1694

Table 1.2: Weekly Total Urea Kt/V - Changes (day 56-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	11	1.316	0.263	0.079	0.760	1.360	1.680
Visit 3 (day 56)	11	1.375	0.244	0.074	1.060	1.350	1.840
Changes (day 56-day 0)	11	0.058	0.340	0.102	-0.380	-0.040	0.820

Changes (day 56-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.7646

Table 1.3: Weekly Total Urea Kt/V - Changes (day 56-day 28)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 2 (day 28)	11	1.424	0.238	0.072	1.070	1.470	1.750
Visit 3 (day 56)	11	1.375	0.244	0.074	1.060	1.350	1.840
Changes (day 56-day 28)	11	-0.049	0.219	0.066	-0.430	-0.010	0.420

Changes (day 56-day 28) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.3613

Table 2.1: Peritoneal Equilibration Test (PET) - Dialysate/Plasma creatinine - Changes (day 28-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	12	0.573	0.130	0.037	0.220	0.600	0.710
Visit 2 (day 28)	12	0.643	0.058	0.017	0.560	0.635	0.740
Changes (day 28-day 0)	12	0.070	0.148	0.043	-0.120	0.040	0.500

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.0322

Table 2.2: Peritoneal Equilibration Test (PET) - Dialysate/Plasma creatinine - Changes (day 56-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	11	0.561	0.128	0.039	0.220	0.590	0.710
Visit 3 (day 56)	11	0.612	0.074	0.022	0.510	0.620	0.700
Changes (day 56-day 0)	11	0.051	0.157	0.047	-0.100	0.040	0.480

Changes (day 56-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.5156

Table 2.3: Peritoneal Equilibration Test (PET) - Dialysate/Plasma creatinine - Changes (day 56-day 28)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 2 (day 28)	11	0.637	0.056	0.017	0.560	0.630	0.740
Visit 3 (day 56)	11	0.612	0.074	0.022	0.510	0.620	0.700
Changes (day 56-day 28)	11	-0.025	0.057	0.017	-0.150	-0.020	0.040

Changes (day 56-day 28) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.2676

Table 2.4: Peritoneal Equilibration Test (PET) - Glucose - Changes (day 28-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	10	0.245	0.098	0.031	0.000	0.270	0.340
Visit 2 (day 28)	10	0.282	0.038	0.012	0.220	0.280	0.340
Changes (day 28-day 0)	10	0.037	0.103	0.032	-0.050	0.015	0.310

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.2695

Table 2.5: Peritoneal Equilibration Test (PET) - Glucose - Changes (day 56-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	10	0.245	0.098	0.031	0.000	0.270	0.340
Visit 3 (day 56)	10	0.295	0.065	0.021	0.220	0.280	0.420
Changes (day 56-day 0)	10	0.050	0.089	0.028	-0.030	0.045	0.270

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.0547

Table 2.6: Peritoneal Equilibration Test (PET) - Glucose - Changes (day 56-day 28)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 2 (day 28)	10	0.282	0.038	0.012	0.220	0.280	0.340
Visit 3 (day 56)	10	0.295	0.065	0.021	0.220	0.280	0.420
Changes (day 56-day 28)	10	0.013	0.069	0.022	-0.080	0.005	0.150

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.6563

Table 3.1: Weekly Total Creatinine Clearance - Changes (day 28-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	12	68.38	16.20	4.68	43.28	67.42	93.39
Visit 2 (day 28)	12	71.09	21.33	6.16	42.38	67.85	105.74
Changes (day 28-day 0)	12	2.71	12.09	3.49	-22.59	2.36	24.79

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.3394

Table 3.2: Weekly Total Creatinine Clearance - Changes (day 56-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	11	69.70	16.30	4.91	43.28	72.22	93.39
Visit 3 (day 56)	11	68.59	20.44	6.16	42.60	65.26	112.38
Changes (day 56-day 0)	11	-1.11	13.17	3.97	-19.70	-1.86	26.86

Changes (day 56-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.5771

Table 3.3: Weekly Total Creatinine Clearance - Changes (day 56-day 28)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 2 (day 28)	11	72.84	21.45	6.47	42.38	69.88	105.74
Visit 3 (day 56)	11	68.59	20.44	6.16	42.60	65.26	112.38
Changes (day 56-day 28)	11	-4.25	11.42	3.44	-21.49	0.14	16.60

Changes (day 56-day 28) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.5195

Table 4.1: Total ultrafiltration (mL) - Changes (day 28-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	12	316.67	271.64	78.42	0.00	300.00	1050.00
Visit 2 (day 28)	12	354.17	264.11	76.24	100.00	300.00	1000.00
Changes (day 28-day 0)	12	37.50	128.14	36.99	-100.00	0.00	350.00

Changes (day 56-day 28) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.5000

Table 4.2: Total ultrafiltration (mL) - Changes (day 56-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	12	316.67	271.64	78.42	0.00	300.00	1050.00
Visit 3 (day 56)	12	483.33	289.46	83.56	0.00	425.00	1150.00
Changes (day 56-day 0)	12	166.67	154.23	44.52	0.00	150.00	400.00

Changes (day 56-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.0039

Table 4.3: Total ultrafiltration (mL) - Changes (day 56-day 28)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 2 (day 28)	12	354.17	264.11	76.24	100.00	300.00	1000.00
Visit 3 (day 56)	12	483.33	289.46	83.56	0.00	425.00	1150.00
Changes (day 56-day 28)	12	129.17	143.75	41.50	-100.00	150.00	400.00

Changes (day 56-day 28) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.0117

Table 5: Weekly Total Urea Kt/V - Comparison BETWEEN Periods (WITHIN patients)

Study Period	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Intervention Period - delta day 0-28	11	0.107	0.251	0.076	-0.160	0.050	0.760
Follow up Period - delta day 28-56	11	-0.049	0.219	0.066	-0.430	-0.010	0.420
Changes (Intervention vs Follow up)	11	-0.156	0.325	0.098	-0.700	-0.230	0.430

Changes (Period 1 vs Period 2) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.1162

Table 6.1: Peritoneal Equilibratione Test (PET) - Dialysate/Plasma creatinine - Comparison BETWEEN Periods (WITHIN patients)

Study Period	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Intervention Period - delta day 0-28	11	0.076	0.153	0.046	-0.120	0.050	0.500
Follow up Period - delta day 28-56	11	-0.025	0.057	0.017	-0.150	-0.020	0.040
Changes (Intervention vs Follow up)	11	-0.102	0.170	0.051	-0.520	-0.060	0.150

Changes (Period 1 vs Period 2)- Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.0225

Table 6.2: Peritoneal Equilibratione Test (PET) - Glucose - Comparison BETWEEN Periods (WITHIN patients)

Study Period	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Intervention Period - delta day 0-28	10	0.037	0.103	0.032	-0.050	0.015	0.310
Follow up Period - delta day 28-56	10	0.013	0.069	0.022	-0.080	0.005	0.150
Changes (Intervention vs Follow up)	10	-0.024	0.150	0.048	-0.350	-0.010	0.200

Changes (Period 1 vs Period 2)- Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.7129

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16. APPENDICES.

16.1 STUDY INFORMATION

16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

Iperboreal Pharma

RESEARCH & DEVELOPMENT DEPARTMENT

Protocol No.: IP-001-09

Efficacy and safety assessments of a peritoneal dialysis solution containing Glucose, Xylitol and L-Carnitine compared to standard PD solutions in Continuous Ambulatory Peritoneal Dialysis (CAPD)

Final Version 3.0 – July 20th, 2010
Revised Version 4.0 - April 28th, 2011 (Amendment 1)
Revised Version 5.0 – January 31st 2018 (Amendment 2)
Revised Version 6.0 – April 01st 2020 (Amendment 3)

CONFIDENTIAL

Approved by **Date**

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Principal Investigator

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The signature of the Principal Investigator on this document represent the participation to the project and provide insurances that:

1. the research will be conducted in adherence to the protocol and complaing with Helsinki Declaration and in accordance with the ICH Note for Guidance on Good Clinical Practice in European Union.
2. any publication relevant to study results will be published or divulged without a written permission from **Iperboreal Pharma S.r.l.**

TABLE OF CONTENTS

ABBREVIATIONS

AC	Acetyl-Carnitine
CAPD	Continuous Ambulatory Peritoneal Dialysis
CAT	Carnitine Acetyl-Transferase
CoA	Coenzyme A
CRF	Case Report Form
ECG	Electrocardiogram
ESRD	End Stage Renal Disease
FC	Free Carnitine
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HD	Hemodialysis
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
i.v.	intravenous
LC	L-Carnitine
CNS	Central Nervous System
Os	orally
PET	Peritoneal Equilibration Test
PD	Peritoneal Dialysis
PDH	Pyruvate Dehydrogenase
QA	Quality Assurance
RBC	Red Blood Cells
SAE	Serious Adverse Event
TC	Total Carnitine
TMF	Trial Master File
WBC	White Blood Cells

1 GENERAL INFORMATIONS

Study protocol No.:	IP-001-09
Title:	Efficacy and Safety assessments of a peritoneal dialysis solution containing Glucose, Xylitol and L-Carnitine compared to standard PD solutions in Continuous Ambulatory Peritoneal Dialysis (CAPD)
Version and data:	Final Version 3.0 – July 20th 2010
	Revised Version 4.0 - April 28th 2011 (Amendment 1)
	Revised Version 5.0 – January 31st 2018 (Amendment 2)
Sponsor:	Iperboreal Pharma S.r.l., - 65122 Pescara (PE) - Italy
Product:	Bags for peritoneal dialysis containing Glucose 0.5%, Xylitol 1.5% and L-Carnitine 0.02% for nocturnal exchanges and Glucose 0.5%, Xylitol 0.7% and L-Carnitine 0.02% for diurnal exchanges

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2 INTRODUCTION

2.1 Background

The uremia (kidney failure) describes a state characterized by the accumulation of uremic toxins leading to multiple organ damage. Renal replacement therapy (dialysis or kidney transplantation) is the recommended treatment modality for patients with advanced chronic renal failure. These patients are known as End-Stage Renal Disease (ESRD) patients.
In current clinical practice, Peritoneal Dialysis (PD) is the preferred method for patients still preserving renal function.
Peritoneal dialysis is based on the solute and fluid exchange between the peritoneal capillary blood and the dialysis solution across the peritoneal membrane. During peritoneal dialysis, a quantity of solution – named PD solution or PD dialysate – is infused into the peritoneum through a catheter.
Continuous Ambulatory Peritoneal Dialysis (CAPD) is a particular technique of peritoneal dialysis consisting in three to five daily exchanges of 0.5 to 3L each, done by the patient itself. During the exchange, the dialysis bag is connected to the peritoneal catheter and the PD solution (usually 2L) is instilled by gravity in 10-20 minutes. Then, the patient can move freely and continues his normal activities. After a dwell period of several hours (usually 4-6 hours), the dialysate is evacuated from the peritoneal cavity via the catheter, also by gravity, and a new quantity of PD solution is instilled instead. In CAPD, the dialysis occurs continuously, 24-hours around.
CAPD is recommended especially in elderly and cardiovascular patients because it assures a stable cardiovascular status, a better control of arterial high blood pressure and steady biochemical parameters. As recently demonstrated, CAPD allows longer preservation of the renal residual function as compared to hemodialysis.
According to its composition, the PD solution can remove or infuse solutes from or to the patient. The solutes are transported across the peritoneal membrane by convection (movement of solutes related to fluid removal) or by diffusion (according to the concentration gradient of the solute between blood and dialysate). Since convection is the main mechanism and fluid removal (ultrafiltration) requires a higher osmolality of the dialysate in relation to serum, all PD solutions contain an osmotic agent.
Many osmotic agents were proposed, but the most used low-molecular weight osmotic agent is glucose. However, the peritoneal membrane is not impermeable to glucose, so that a rapid reduction of the osmotic gradient and an increase of serum carbohydrates are seen in CAPD patients. Almost 50-60% of the instilled glucose into peritoneal cavity is absorbed during a usual dwell time (4-6 hours). About 100-300g/day of glucose are absorbed when the used glucose concentration in PD solutions is 1.5%-4.5% (1-6).
Glucose has long-term detrimental effects on the peritoneum, which ultimately may result in ultrafiltration failure of the peritoneal membrane. Furthermore, absorption of the glucose from dialysate enhances the disturbances of carbohydrates metabolism, which is already impaired in uremic state. Advanced chronic renal failure is associated with insulin resistance and disorders of glucose, lipids and amino acids homeostasis. (7-9)
Compared to hemodialysis, in CAPD patients a higher *à jeun* level of serum insulin, an augmented response to insulin at every dialytic exchange and an elevated 24-hour profile of insulin are found. (2) A high level of hyperglycemia is observed in patients treated with higher doses of glucose, but a slight hyperglycemia and hyperinsulinemia occur in all CAPD patients. (10)
In CAPD patients were reported more frequent diabetes mellitus and hyperlipidemia (especially hypertriglyceridemia and abnormalities of serum lipoproteins), partially accounted for by the glucose absorption. (3, 4, 5, 11-16). Although in the general population with healthy kidney function an altered lipoprotein profile is believed to increase the risk of cardiovascular disease, in dialysis patients (HD and PD) this is much less evident. Actually, it has clearly been shown that (a) an inverse relationship between survival and hyperlipidemia (high LDL-cholesterol or triglycerides)

there exist in dialysis patients, and that (b) statin treatment does not offer any survival benefit in both diabetic and non-diabetic dialysis patients with altered lipid profile (17-19).

2.2 Pharmacology

2.2.1 Biological, pharmaco-metabolic and safety properties of L-Carnitine

Biological properties

L-Carnitine (LC) is a naturally occurring substance involved in the translocation of long-chain fatty acids across the mitochondrial membrane. The roles of carnitine in regulation of the fatty acids oxidation, ketogenesis and production of cellular energy are well known. (20-24).

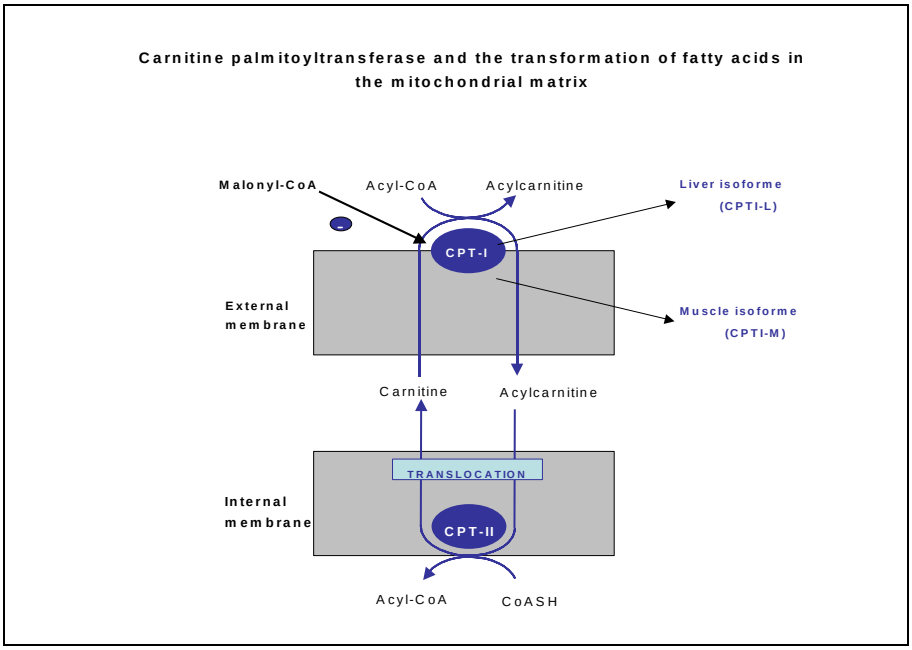


Figure 1. The involvement of carnitine in fatty acids transformation in the mitochondrial matrix

Cytosolic long-chain fatty acids, which are present as CoA esters, are trans-esterified to L-carnitine in a reaction catalysed by carnitine palmitoyltransferase I (CPT I) at the mitochondrial outer membrane (**Figure 1**). In this reaction, the acyl moiety of the long-chain fatty acids is transferred from CoA to the hydroxyl group of carnitine. The resulting long-chain acylcarnitine esters are transported over the inner mitochondrial membrane via a specic carrier, carnitine-acylcarnitine translocase (CACT). At the matrix side of the mitochondrial membrane, the long-chain fatty acids are transesterified to intramitochondrial CoA, a reaction catalysed by carnitine palmitoyltransferase II (CPT II). The released carnitine can then leave the mitochondrion via CACT for another round of transport. In the mitochondrial matrix, the enzyme carnitine acetyltransferase (CAT) is able to reconvert short- and medium-chain acyl-CoAs into acylcarnitines using intramitochondrial carnitine. These acylcarnitines can then leave the mitochondria via CACT. In addition, LC is able to modulate the intra-mitochondrial pool of free acetyl-CoA and CoA, through the action of carnitine acyl-transferase (CAT). Elevated acetyl-CoA levels in mitochondria are known to inhibit enzymes involved in glucose metabolism such as pyruvate dehydrogenase (PDH).

Pharmaco-metabolic properties

A large body of experimental evidence indicates that LC exerts *in vitro* and *in vivo* pharmacological actions at concentrations significantly higher (low millimolar range) than those physiologically present in the extra- and intra-cellular milieu (low micromolar to low millimolar range) [see also 24].

Given the very poor pharmacokinetic properties of LC (very low bioavailability, very efficient kidney excretion, etc), the achievement of a LC plasma and target organ exposure to elicit the expected pharmacological response should be feasible in PD patients rather than in patients with a normal kidney function. Indeed, it is well known that intravenous LC supplementation to HD patients results in more than five fold increase of LC plasma concentration (i.e., 20 mg/kg given at the end of each dialytic session for 12 weeks), whereas a comparable dosage of LC, orally supplemented to subjects with an healthy kidney, modestly increases plasma LC levels (25). It should also be noted that PD patients, as well as HD patients, have lower free LC plasma levels, LC deficiency, along with an altered ratio of free vs acyl-carnitines, LC insufficiency (26-28). Thus, in addition to potential pharmacological actions (seel also below), LC administration would also correct LC deficiency in PD patients.

The work published by Ferranini et al. is probably the most convincing and detailed evidence on the action of LC on glucose consumption in healthy human volunteers (29). During a short term euglycemic hyperinsulinemic clamp, intravenous LC infusion was administered to achieve a steady four-fold increase in basal serum LC levels. Exogenous LC infusion was associated with a statistically significant increase of whole body glucose utilization and this effect was more pronounced in the subjects with higher rates of glucose disposal. Since net rates of insulin-induced glucose oxidation were similar with or without LC, the LC-induced enhancement of total glucose metabolism was quantitatively accounted for by a 50% increase in non-oxidative glucose disposal. In addition, plasma acety-L-carnitine levels significantly increased during LC infusion, suggesting that the administration of exogenous LC was able to affect the intra-mitochondrial pool of acetyl-CoA.. Using a similar experimental protocol and clamp technique, Mingrone et al have later reported that even in diabetic subjects the intravenous LC infusion increases glucose consumption (30). These studies unambiguously demonstrated that LC stimulates muscle glucose consumption by relieving acetyl-CoA inhibition of PDH. Indeed, in skeletal muscle of diabetic and/or insulin resistant subjects, insulin appears to be unable to mediate the switch from lipid to carbohydrate oxidation, a state described as “metabolic inflexibility” [24]. The fasting diabetic/insulin resistant muscle is characterized by a blunted suppression of glucose oxidation and lower than normal rate of fatty acid oxidation, and in the fed state insulin is less able to stimulate muscle glucose oxidation. One of the components of the pathogenetic mechanism responsible for the impaired muscle glucose disposal observed in diabetic/insulin resistant patients may be associated with PDK activation by an increased size pool of intramitochondrial acetyl-CoA which would act synergistically with the increased expression of specific isoforms of PDHK, e.g. PDHK4 [31].

In ESRD patients, Gonal et al have shown that a single i.v. administration of LC improves insulin sensitivity as evaluated by an insulin tolerance test [32]. Biolo et al. in a randomized, matched-paired, double-blind, placebo controlled experimental design determined the capability of chronic intravenous LC supplementation in modifying insulin resistance and protein catabolism in non-diabetic HD patients [33]. LC treatment led to a statistical significant reduction of leucine oxidation rates and appearance from proteolysis during the clamp studies compared to the placebo group. Insulin-mediated glucose disappearance was significantly improved by LC only in those patients with greater baseline insulin resistance, selected according to the median value of insulin sensitivity before treatment. A more recent study have addressed the effects of 24-week oral acetyl-L-carnitine (1 g twice daily) therapy, an LC prodrug, on the glucose disposal rate (GDR), assessed by hyperinsulinemic euglycemic clamps, and components of the metabolic syndrome in nondiabetic subjects at increased cardiovascular risk a priori segregated into 2 groups with high GDR values (insulin-sensitive) and low GDR values (insulin-resistant), respectively [34]. Acetyl-L-carnitine treatment significantly increased GDR and improved glucose tolerance in patients with low GDR values (insulin-resistant), whereas it had no effects in those with higher GDRs.

Although the clinical studies described above did not attempt to evaluate the potential action of L-carnitine on hepatic glucose production in the diabetic condition, some clues may be found in a number of preclinical studies conducted on diabetic experimental models. In a study originally designed to evaluate the beneficial action of L-carnitine on diabetic heart [35], streptozotocin-treated diabetic rats were dosed for 6 weeks with a very high daily intraperitoneally dose of LC (3g/Kg); at the end of the treatment, the L-carnitine group showed a remarkable reduction of plasma glucose compared to diabetic control group. Importantly, the lowering of plasma glucose was associated with the reversal of both glucosuria and polydipsia. L-Carnitine treatment of non-diabetic rats did not affect plasma glucose levels [35]. Taking into account that L-carnitine treatment did not affect the hypoinsulinemic state of streptozotocin diabetic rats, and that in this diabetic model the severe hyperglycaemic state is mainly driven by an increased hepatic glucose production, it is possible that L-carnitine could have been acting, at least partly, through the inhibition of gluconeogenesis. Further evidence of the anti-gluconeogenic action of pharmacological doses of L-carnitine has recently been provided by Rajasekar & Anuradha [36]. In this study, Wistar rats were fed for 1 month with fructose as the sole source of carbohydrate, an experimental model characterized by a severe impairment of insulin sensitivity, glucose intolerance, dyslipidemia and increased hepatic glucose production. Intraperitoneal L-carnitine administration (300 mg/kg/24h) for the entire period of fructose feeding normalized the elevated plasma glucose and insulin levels, and liver TG and FFA content in fructose fed rats [36]. These authors suggested that the ability of L-carnitine treatment to mitigate the adverse effects of the fructose diet was mainly due to the correction of L-carnitine deficiency induced as a result of the fructose load. If their interpretation is correct, it is possible that L-carnitine depletion in the liver could have affected FFA oxidation and, hence, the metabolic partitioning of long-chain fatty acyl-CoA towards esterification, leading to steatosis and increased hepatic VLDL-triglyceride secretion. Amelioration of insulin-stimulated glucose disposal in an obese diabetic transgenic mouse model was obtained after a 3 week period of dietary L-carnitine supplementation (1g/kg/day) [37]. Withdrawal of L-carnitine treatment for 6 weeks re-established the original diabetic state, though a further week of L-carnitine treatment reversed the loss of insulin sensitivity. After this second treatment period with L-carnitine, fasting glucose levels were strongly reduced, implying that L–carnitine therapy could have improved hepatic insulin sensitivity and, hence, the insulin-suppressive action on hepatic glucose production in this diabetic mouse model [37]. In addition, it may be worth noting two recent clinical papers reporting on the efficacy of LC treatment in lowering Lp(a) in hypercholesterolemic (38) and newly diagnosed diabetic patients (39).

Taken together, these observations suggest that LC administration at pharmacologic levels could be beneficial in improving the altered glucose and lipid homeostasis in PD patients.

Safety properties

The toxic effects of the intraperitoneal administration of LC were investigated in mice and rats. The DL50 is 12g/kg in mice and 8g/kg in rats, respectively (study performed in 1982 - first introduction of the GLP). With doses of 6.3g/kg in mice and 7g/kg in rats, no adverse events were observed in all the animals. More recent, another two studies regarding the peritoneal and systemic tolerability were performed on Sprangue Dawley rats. The first one consisted in a single intraperitoneal dose of LC in 2mL standard solution of glucose. Three different concentrations were tested: 0.75%, 7.5% and 15% corresponding to doses of 15, 150 and 300mg/kg, respectively. The second study investigated rats treated for 7 consecutive days with intraperitoneal administration of LC in a standard solution of glucose, in different concentrations (0.75%, 7.5% and 15%) corresponding to doses of 15, 150 and 300mg/kg, respectively.

Finally, in order to evaluate the local tolerability, a third experiment was conducted in rabbits, which received a single subcutaneous dose of LC diluted with 1mL standard solution of glucose, using the same different concentrations (0.75%, 7.5% and 15% corresponding to doses of 15, 150

and 300mg/kg, respectively). These studies on toxicity and tolerability indicated that LC is well tolerated even in high doses.
Two different clinical studies were performed in CAPD patients by adding LC in the PD solution. Bazzato et al. demonstrated that a dose of 2g of LC, added to PD dialysate and administered during the nocturnal exchange, was well tolerated, restoring the level of LC and augmenting the lipid pattern in 6 from 7 treated patients. (40)
Kopple, in a clinical trial on 5 CAPD patients who received 20mg/kg LC in PD solution at 8 a.m. for a period of 14 days, showed an improvement of nitrogen balance after the administration of LC and, also, a good tolerability (41).
Other two studies assessed the effects of L-Carnitine in hemodialysis (HD) patients. During the first study, LC was intravenously infused in a dose of 2g at the end of every hemodialysis session, three times weekly for 12 months (42), while in the second study a dose of 40mg/kg LC was infused at the end of every HD session, three times weekly for 6 months (43). The serum concentrations of total and free carnitine reached were 1297±256µmol/L and 756±336µmol/L in the first study, and 790±229µmol/L and 455±162µmol/L in the second study, respectively. Since in both studies no adverse events were found, we can conclude that LC is well tolerated even when very high plasmatic levels are obtained (100 times higher than physiological concentrations).
In a recent study on 4 CAPD patients, Bonomini et al. added LC in the PD solution bag for the nocturnal exchange (44). The patient's dialytic schedule consisted of 4 daily exchanges: 3 during the day and 1 during the night with PD solution containing 2.27% glucose. The osmotic properties between the 2.27% glucose solution bag used for nocturnal exchange and the 1.36% glucose solution bag supplemented with 5 grams (0.25 % w/v) of LC were compared. Parameters of dialysis efficacy (Kt/V, peritoneal equilibration test, creatinine clearance), ultrafiltration, diuresis, and body weight were assessed during the observation period (7 days before the first supplementation with LC) and the therapeutic period (5 consecutive days with nocturnal exchange performed with 5 grams of LC added to a 1.36% glucose solution bag). Also, the carnitine concentration in plasma, urine and peritoneal effluent from all the exchanges were determined. The daily ultrafiltration volume was stable, without significant individual variations. The study provided interesting results: the diuresis was preserved without significant variations, and the ultrafiltration (UF) obtained during the exchange with PD solution supplemented with LC was comparable with that resulting from the exchange performed with 2.27% glucose solution (showing even an improvement trend). Such similar results concerning UF were confirmed by the lack of variation in patients' body weight. The tendency of augmented ultrafiltration capacity of the bag supplemented with LC varied from 5% to 13%. As expected, the carnitine plasma level at the end of the study was increased within a tolerable pharmacological range and the steady state was reached in the fourth day of treatment. After reaching the stable level, the plasma concentration of free carnitine was around 1.2mM. From the total dose of carnitine administered during the five days of treatment, over 75% was removed through the main elimination routes. It should also be noted that LC concentration that will be used in the current proposed clinical trial will be 12.5 fold less (0.02%. w/v) than the one used in the above described clinical trial (0.25%, w/v).
Two additional clinical trials with PD solutions containing LC are in progess in diabetic and non diabetic patients with ESRD in CAPD (ClinicalTrials.gov Identifier No NCT00755404 and NCT00755456, respectively)
No adverse reactions were noticed in all the above clinical trials mentioned suggesting a good tolerability of LC administration.

2.2.2 Biological, pharmaco-metabolic and safety properties of Xylitol

Biological properties

Xylitol is a five-carbon sugar alcohol, pentitol, which is manufactured by the reduction of D-xylulose. Xylitol is widely distributed in the plant and animal kingdoms. It is present in most wines

as a fermentation product and in significant quantities in plums, strawberries, cauliflower, raspberries, etc. (45). In plums, approximately 1% of the dry weight is xylitol.
In mammals, the metabolism of xylitol varies according to the origin and of route of administration. Approximately 5-15 g of xylitol are formed per day in the human body, based upont he observationt hat similar amounts of L-xylulose are excreted daily in urine in patients with essential pentosuria (46). Xylitol fed orally, depending on dosage, may not be totally absorbed. However, adaptation appears to occur in humans. This adaptation is most likely due to the transition of intestinal flora contents rather than to other biochemical mechanisms (47). Unlike glucose, xylitol is most likely absorbed by intestinal mucosa through passive or facilitated diffusion. Therefore, the rate of xylitol absorption is far slower than that of glucose. Liver is the major site for removal of either oral or intravenous xylitol. The liver appears to be responsible for 50-80% of xylitol metabolism in normal conditions. Some 15-20% of the remaining amount of parenterally administered xylitol can be used extrahepatically in the kidney, lung, erythrocyte, fat stores, and myocardium (46). The distribution of xylitol in eviscerated rats was found to be insulin independent. The removal of xylitol from blood appeared to be first-order kinetic process with a half-life of 19-23 minutes for non-adapted human adults, whereas its excretion is by simple glomerular filtration, and there is no readsorptive mechanism for it (46).
Xylitol is first oxidized to D-xylulose by the NAD-xylitol dehydrogenase, causing the NADH/NAD ratio to increase (see scheme below). The next step is the phosphorylation of D-xylulose to D-xylulose-5-phosphate by D-xylulose-kinase. D-xylulose-5-phosphate is an intermediate of the pentose phosphate shunt and it is metabolized to fructose-6-phosphate and glyceraldehyde phosphate by this pathway. Three molecules xylitol yield two molecules of fructose-6-phosphate and one molecule of glyceraldehyde phosphate. Fructose-6-phosphate can readily be converted to glucose and glycogen; glyceraldehyde phosphate either to glucose, glycogen or lactate. Most of the xylitol is rapidly converted to glucose and glycogen, and only small quantities are converted to lactate (**Figure 2**).

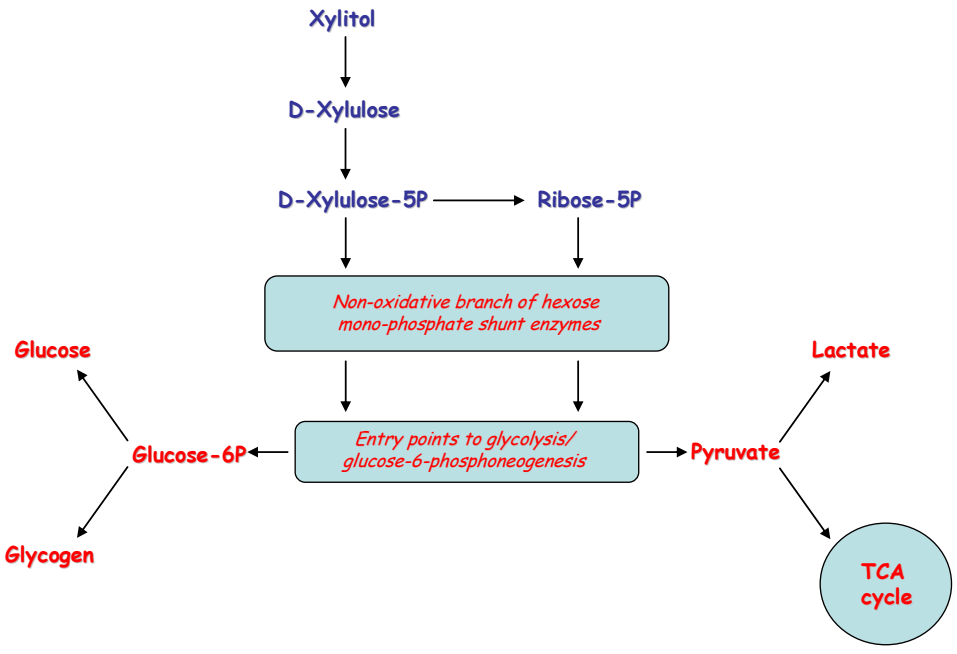


Figure 2. The metabolic fate of Xylitol

Pharmaco-metabolic properties

Parenteral nutrition is used clinically to optimize fluid, energy, nitrogen, electrolyte, and vitamin balance, especially in patients in shock, in a coma, with trauma, undergoing major surgery, or having burns, sepsis, diabetes, cancer cachexia, or acquired immunodeficiency syndrome (AIDS).

These conditions are often characterized by suppressed insulin secretion or by hyperinsulinemia and insulin resistance, with consequent impaired glucose utilization (48). Indeed, infusions of glucose as an energy source in these conditions often require careful monitoring of blood glucose and the concomitant administration of insulin. Xylitol has been recommended as a parenteral nutrient because its entry into cells is insulin-independent, it is efficiently utilized after its intravenous infusion (without serious hyperglycemia), it stimulates less insulin secretion than does glucose, and it is less of an irritant to veins than is glucose when given in hyperosmolar solution (49).
Since 1970, it has been used in diabetics and for parenteral nutrition as a glucose substitute. It is also largely used at oral level in order to prevent the dental cavities since is able to form a complex with calcium stabilizing the salivary calcium-phosphate system. Xylitol has also been used as an osmotic agent in peritoneal dialysis showing some advantages over glucose: a better control of glycemia, enhancement of the endogenous insulin secretion and reduction of the administered insulin dose (50).
Xylitol has been used in Germany as a sugar substitute of glucose in total parenteral nutrition (see Totufusin OPX and ELKO-Mix, Baxter; Aminomix 4, Fresenius Kabi; Nutriflex Combi, BBraun) and the Ministry of Health authorized a maximal dose of xylitol of 3g/kg/day. These xylitol-based infusional products contain either xylitol alone or in combination with various nutrients (aminoacids, sugars, etc.).
Buoncristiani et al. assessed the use of xylitol as partial substitute of glucose in peritoneal dialysis bags (51). The observed benefits of these two sugars association were a lower 24-hours glycemic curve and a reduced response of insulin. Also, the lipid metabolism seemed to be improved and an increase of serum protein and albumin was found. Two patients who have used xylitol in PD solution were treated by peritoneal dialysis for 10 years and the only problem they experienced was a slight increase in serum uric acid levels.
Recently, Buoncristiani et al. investigated in vitro the biocompatibility and toxicity of a solution containing xylitol in different concentrations compared to glucose (52). The following effects were described:

1. Increase of the rabbit's mesothelial cells in the presence of solutions with low-glucose content or in complete absence of glucose.
2. In a single layer of mesothelial cells, the greater toxicity resulted from solutions without xylitol. Indeed, IL-1, expressed as a result of cellular injury, was increased in cells with higher levels of glucose. Conversely, PGI_2, expression of minor lesions, decreased with lower glucose concentration.
3. At the level of mesothelial cells, the concentrations of phospholipids and phosphatidil-choline, indispensable surfactants for normal functioning peritoneum, were higher in presence of xylitol.
4. The minor formation of giant cells suggested a scarce toxicity and a good biocompatibility of solutions without glucose.

The scarce toxicity and good biocompatibility of xylitol were demonstrated in various clinical trials that used parenteral administered xylitol.
A clinical trial conducted by Bazzato et al. investigated xylitol as an osmotic agent replacing glucose in end-stage renal disease insulin-dependent diabetics on CAPD (50). The therapeutic schedule, followed for a median duration of 8.7 months (range 5-11 months), consisted in 4 daily exchanges of 2L PD solution, from which 3 were with normal osmolality solution (Xylitol 1.5g/dL) and one with hyperosmolar solution (3g/dL). The total daily dose of xylitol administered via peritoneum with this protocol was 150g. The plasma xylitol level was 30mg/dL during the daily dwells and reached 80mg/dL during the nocturnal dwell. These concentrations had no influence on plasma osmolality.
In treated patients, it was noticed a significant improvement of lipid profile: triglycerides and cholesterol levels decreased after the first two months of treatment, while HDL-cholesterol increased, restoring the normal levels after 2-5 months. All these parameters remained until the end

of the study. The elevated plasma levels of inorganic phosphorus observed during CAPD with glucose were significantly reduced 5 months after the commencement of the CAPD with xylitol. The required exogenous insulin was reduced to half as compared to the amount administered during CAPD with glucose. The level of glycosilated hemoglobin was significantly lower during treatment with xylitol as compared to the therapeutic period with glucose, indicating a better control of diabetes mellitus.
During the observation period, a progressive increase of serum uric acid concentration was seen, requiring administration of allopurinol that induced a slow reduction of these values.
Lactic acid was enhanced during the entire treatment period, remaining however within normal range.
The dosage of 150g/day xylitol was well tolerated, without evidences of adverse effects or clinical signs of calcium oxalate deposition (50). Only when the xylitol dosage exceeded 150g/day, in patients who needed PD solutions with higher content of xylitol in order to augment the ultrafiltration effect, adverse events like nausea, vomiting or increased levels of serum bilirubin and transaminases occurred.
It should be mentioned that in our study the patients would be exposed to a maximum xylitol dosage of 36g/day, a value lesser than that used by Buoncristiani (55 g/day) and much less than that used by Bazzato (150 g/day) (50-52).

Safety properties

In 1986, the Federation of American Societies for Experimental Biology (FASEB) was commissioned by the U.S. Food and Drug Administration (FDA) to review all relevant data concerning xylitol and other polyols (www.cfsan.fda.gov/~lrd/fr960823.html). The FASEB report's scientific conclusions indicate that the use of xylitol in humans is safe. The report also affirms xylitol's acceptability as an approved food additive for use in foods for special dietary uses.
In 1996, the Joint Expert Committee on Food Additives (JECFA), a prestigious scientific advisory body to the World Health Organization and the Food and Agricultural Organization of the United Nations, confirmed that adverse findings in animal studies conducted in the 1970s are "not relevant to the toxicological evaluation of these substances (e.g., xylitol) in humans." JECFA has allocated an Acceptable Daily Intake (ADI) of "not specified" for xylitol. ADI, expressed in terms of body weight, is the amount of a food additive that can be taken daily in the diet over a lifetime without risk. An ADI of "not specified" is the safest category in which JECFA can place a food additive. The Scientific Committee for Food of the European Union (EU) also determined xylitol "acceptable" for dietary uses.
However, since it has been reported in the literature that xylitol infusion may increase lactate, urate and oxalate levels, which in turn may have potential side-effects, a thorough reappraisal of this issue in relationship to the use of xylitol in PD is reported below.
Lactate: In the Bazzato's paper, where the daily dose of xylitol administered intraperitoneally was 150 grams, serum lactate levels after 11 months of xylitol treatment were 17.5 mg/dL compared to 12.6 mg/dL before xylitol treatment (50). Since the normal plasma range of lactic acid is 6.7-21.6 mg/dL (Scientific tables Geigy), the modest increase observed remains within normal range. In the Buoncristiani experience, where the daily dose of xylitol administered intraperitoneally was 55 grams (almost 3 fold less than Bazzato), serum lactate levels after years of xylitol treatment were comparable to PD patients treated with glucose as an osmotic agent (52). Since we are planning to use lower (long exchange) or similar (short exchange) amounts of xylitol compared to that used by Buoncristiani, potential elevation of lactic acid in plasma is not an issue. It should be taken into account that even glucose infusion (i.v. or i.p.) may lead to increased plasma levels of lactic acid, which, under certain circumstances (thiamine deficiency), it may reach extremely high levels, leading to metabolic acidosis (53). In the PubMed there are several cases of severe lactic acidosis in thiamine deficient patients exposed to glucose given as a parenteral infusion.

Thus, even in the classic PD solution containing only glucose, it would not be a bad idea to either include in the bag or to treat PD patient with some thiamine, in order to improve acid-base homeostasis in PD patients. In principle, PD patiens are prone to develop mild thiamine deficiency.

Urate: Elevated serum uric acid has been suggested as a feature of hyperinsulinemia and insulin resistance (54). Although a number of studies have further evaluated increased serum uric acid as a component of the Metabolic Syndrome, there is currently no satisfactory explanation for the relation of uric acid and the syndrome. This is of particular interest, since it has been suggested that the still disputed relationship between elevated uric acid and cardiovascular disease could be secondary to its association with obesity, dyslipidemia, and hypertension. In addition, a number of epidemiological studies, in particular the one that has revisited the well-known Framinghan Heart Study, have shown that uric acid does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes (55). On the other hand it has been suggested that high plasma urate concentrations may decrease the risk of Parkinson's disease, and they raise the possibility that interventions to increase plasma urate may reduce the risk and delay the progression of Parkinson's disease (56).
Administration of high daily doses of xylitol may provoke an increase in the serum uric acid concentration. This seems to result from an augmented purine biosynthesis, due to enhanced formation of ribose phosphate (see role of the hexose monophosphate shunt in providing sugars for nucleic acids). In the Bazzato's paper, where the daily dose of xylitol administered intraperitoneally was 150 grams, serum urate levels after 11 months of xylitol treatment were 9.1 mg/dL compared to 5.6 mg/dL before xylitol treatment (50).
Thus, considering that the normal plasma range of urate is 3.0-7.1 mg/dL (Scientific tables Geigy), xylitol treatment seems to modestly increase urate levels above the normal range. In the Buoncristiani experience, where the daily dose of xylitol administered intraperitoneally was 55 grams (almost 3 fold less than Bazzato), urate levels after years of xylitol treatment were slightly elevated compared to PD patients treated with glucose as an osmotic agent (52). However, such elevation remained within the normal range (Buoncristiani, personal communication).
Since we are planning to use lower amounts of xylitol compared to that used by Buoncristiani, potential elevation of uric acid in plasma is not an issue.

Oxalate: This compound is present in many plants, such as tea and green leafy vegetables, but very little is absorbed through the gastrointestinal tract. The colon is believed to be the major site of reabsorption. Oxalate is excreted exclusively in the urine as an end product of metabolism. There is no evidence to suggest that oxalate is metabolized in humans. Under normal conditions, urinary oxalate is derived primarily from glyoxalate, ascorbic acid, and dietary oxalate (**Figure 3**). Oxalate forms a wide variety of salts, the most important of which is calcium oxalate.

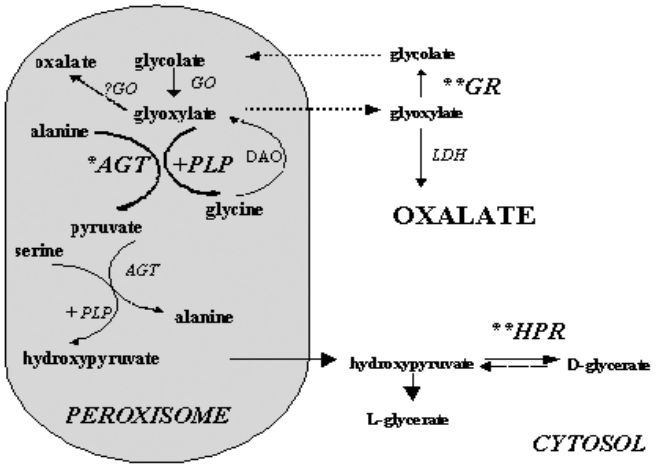


Figure 3. The metabolism of oxalate

The pathogenesis of oxalosis (primary and secondary) may be related to its poor water solubility. Indeed, nephrotoxicity of oxalate is believed to be related to a direct toxic effect on the renal tubules and interstitium, as well as to the development of oxalate stones.

Primary oxalosis is a multiorgan disease that results from calcium oxalate deposition in multiple tissues. Primary hyperoxaluria is a very rare congenital disease (incidence rate about 1.2/10,000,000 per year). It is inherited as an autosomal recessive trait and is characterized by the deficiency of the enzyme glyoxylate aminotransferase as in Type I primary hyperoxaluria and the enzyme D-glyceric dehydrogenase as in Type II (57). Renal oxalate deposits are found primarily in the proximal tubules, and the natural history of this disease is the development of renal failure secondary to massive oxalate deposition in the kidneys. Renal transplantation is often complicated by recurrence of the disease, and a combined kidney and liver transplantation has been suggested by many to be the procedure of choice for primary hyperoxaluria Type I.

Secondary oxalosis is the result of excessive oxalate accumulation because of increased ingestion, increased production, or decreased excretion induced by exogenous factors. Two compounds, ethylene glycol (58) and methoxyflurane (59), that cause increased oxalate production, marked hyperoxaluria, and renal oxalate deposition, are well-known causes of acute renal failure. Renal insufficiency attributed to oxalate deposits has been reported with massive administration of vitamin C (60).

Recently, it has been reported a case of acute renal failure following xylitol infusion in a patient with previously unknown primary hyperoxaluria type 1 (61). A case of oxalate-induced lethal encephalitis (62) and fatal cerebrorenal oxalosis (63) have been reported in patients receiving parenteral infusion of various sugars (sorbitol, fructose, xylitol, etc) above the recommended dosages. There are few other cases of cerebro-renal oxalosis reported in the PubMed, though the casual relationship with xylitol infusion is quite dubious (presence of primary oxaluria, infusion of xylitol with other sugars including glucose, increased endogenous oxalate production in TPN patients, etc). In addition, according to Baxter Germany, no fatal cases resulting from Tutofusin OP X, a common infusion solution containing xylitol (50 grams per liter), has been reported so far (personal communication). Tutofusin OP X is in the market since several years and is largely used (half a million of bags sold per year). It should be noted that several other Companies containing xylitol alone or in combination with other ingredients (aminoacids, sugars, etc) have been registered in Germany as infusional products for total parenteral nutrition (Deltaselect, BBraun, Fresenius Kabi, Serag Wiessner).

From the metabolic standpoint, the formation of oxalate from xylitol as well as glucose is a minor pathway. Hauschildt et al have shown that in patients treated with parenteral infusion containing

xylitol, the concentration of oxalate in the blood and the excretion of oxalate in the urine did not exceed the normal range in any patient (64). In addition, McWhinney et al. have shown no evidence of abnormal fluxes through the two-carbon pathway to oxalate, nor of hyperoxaluria in normal and recurrent stone formers subjects as related to xylitol infusion (65). Interestingly enough, an oral glucose load leads to a significant increase of calcium and oxalate excretion in the urine (66).
In the Bazzato's paper, where the daily dose of xylitol administered intraperitoneally was 150 grams, no clinical signs of calcium oxalate deposits, which would have worsened cerebral or residual kidney function, were noted throughout the treatment (50). In the Buoncristiani experience, where the daily dose of xylitol administered intraperitoneally was 55 grams (almost 3 fold less than Bazzato), no clinical signs of calcium oxalate deposits were noted and plasma oxalate levels were comparable to PD patients using glucose as the only osmotic agent (52).

2.2.3 Biocompatibility of peritoneal dialysis solutions containing glucose, xylitol and LC

LC and xylitol are extremely stable naturally occurring chemical compounds. For example, both compounds are thermally stable even at temperatures higher than those used to steam-sterilize infusional product (50, 67). They are thermally stable in aqueous solutions buffered either in an acid, neutral or alkaline pH. LC or xylitol have safely been combined with many different nutrients for the development of total parenteral solutions and peritoneal dialysis solutions (PDS) (see also above). As expected, preliminary stability studies conducted on the two PDS that we have planned to use for our clinical trial are demonstrated to be chemically and physically stable. The composition of our two PDS is the following: product code IPX15 contains glucose (0.5%), xylitol (1.5%) and LC (0.02%), and product code IPX07 contains glucose (0.5%), xylitol (0.7%) and LC(0.02%). In addition, both products contain the following salts: NaCl 5.786 g/L, $CaCl2 \cdot 2H2O$ 0.257 g/L, $MgCl2 \cdot 6H2O$ 0.102 g/L, sodium D/L-lactate 3.925 g/L. Both solutions are buffered at pH 5.5. The calculated osmolality of the two PD solutions are equivalent to the traditional 1.5% and 2.5%, glucose-based, PD solution. It is worth to mention that although xylitol and glucose are sugars, the former can be steam-sterilized in a wide range of pH without any risk of non-enzymatic oxidation, one of the main causes of glucose-mediated peritoneal damage (see also below). Indeed, reducing sugars such as glucose, oligosaccharide and polyglucose containing carbonyl groups in the sugar unit react with free amino groups of aminoacids and protein in a complex series of reactions known as the Maillard reaction. Since sugar alcohols or polyols such as xylitol do not participate in the Maillard reaction, xylitol represent a better alternative than glucose as an osmotic ingredient both from the manufacturing and biocompatibility standpoints (see also above).

Biocompatibility of Peritoneal Dialysis Solutions

The biocompatibility of a PDS may be defined as its capacity to leave the anatomical and functional characteristics of the peritoneum unmodified in time (68,69). In this context, challenging primary mesothelial cells with PDS is believed to be the gold-standard *in vitro* approach to asses the peritoneal biocompatibility of such solutions (68-70).

Mesothelial cells are specialized epithelial cells that line the serous cavities (pleural, pericardial, and peritoneal) and internal organs. Their primary function is to provide a nonadhesive frictionless protective barrier that facilitates movement of opposing tissues and organs within the serous cavities. Once considered to be passive cells, there is now compelling evidence to highlight their critical role in antigen presentation, inflammation, wound healing, and transport of fluids and cells across the serosal cavities (71,72). Mesothelial cells modulate the microcirculation by their ability to secrete vasodilators, such as prostaglandins and nitric oxide, or vasoconstrictors, such as endothelin. Furthermore, these cells elaborate fibrinolytic molecules to prevent fibrous adhesions have phagocytic properties that participate in defense against infections, and are capable of synthesizing a plethora of macromolecules and peptides that contribute to the structural and functional integrity of the underlying basement membrane

and the chemotactic gradient responsible for the recruitment of monocytes and neutrophils. Peritoneal mesothelial cells cultured in vitro possess the same immunohistochemical markers as peritoneal mesothelial stem cells, and thus they provide a pertinent in vitro model to study the effects of various agents and stimuli on cellular functions such as proliferation, viability, and protein synthesis (73).

It has soon become apparent that the currently used PDS are limited in terms of biocompatibility. Many studies have convincingly demonstrated the adverse effects of peritoneal dialysis solutions toward peritoneal membrane and peritoneal host defense (74–80). One of the aspects of peritoneal dialysis solutions that has been viewed as bioincompatible is the presence of glucose, which is added in high concentrations to most PDS as an effective osmotic agent. Both the development of "*diabetiform*" alterations in peritoneal ultrastructure in patients undergoing CAPD (81-84) and the impaired function of cells exposed to glucose-based PDS (78,85) have been linked either directly or indirectly to the use of glucose. These effects may be related to the metabolic action of glucose *per se*, the corresponding rise in osmolality, the accumulation of glycated proteins, and/or the formation of glucose degradation products (86).

At this regard, we have recently published two studies (87, 88) where we have examined the growth and function of primary rabbit peritoneal mesothelial cells cultured in the presence of various PDS containing either glucose alone, glucose and LC, xylitol and glucose, or xylitol, glucose and LC (see the exact composition of the various PDS and related acronyms in the Appendix). Glucose was present at two different concentrations (1.36 and 3.86 %, w/v). LC also was present at two different concentrations (0.05 and 0.2 %, w/v). Xylitol concentration, instead, was kept fixed at 1% (w/v). The biocompatibility of the PDS was evaluated according to various well-established growth and functional assays (68-70):

1. *Growth of mesothelial cell cultures*
2. *Secretion of phospholipids (PLPs) and phosphatidylcholine (PC) by mesothelial cells*
3. *Secretion of Prostaglandin E2 (PgE2) by mesothelial cells*
4. *Lactic dehydrogenase (LDH) release by mesothelial cells*

Highlights

Our study comparing the effects of PDS containing glucose alone with or without LC, and glucose and xylitol with or without LC on cultured mesothelial cells led to the following findings (85).

1. Mesothelial cells grew much better in PDS containing LC than in those PDS not containing it. In the glucose-xylitol PDS containing LC, mesothelial growth was higher than in those containing glucose and LC. Indeed, the lower the amount of glucose the better the growth. However, the presence of LC always showed an improvement of mesothelial growth.
2. Phospholipid secretion of mesothelial cells was much higher when LC was present in PDS. This is an important index of cell function, as phospholipids are essential for peritoneal physiology. Secretion of phosphatidlycholine, the most active mesothelial surfactant, was indistinguishable between cells cultured in medium with LC, (particularly XGC-2) and controls. Significantly lower secretion was observed with medium containing high glucose levels.
3. As a general index of cytotoxicity, LDH secretion by mesothelial cells was higher in media with PDS containing glucose alone and glucose plus xylitol than the respective PDS with LC.
4. Prostaglandin E2 secretion was significantly higher in media containing LC.

Collectively, these data suggest the addition of LC to various combinations of sugars render PDS more biocompatible. Overall, the best combination examined resulted to be the glucose-xylitol-LC.

2.3 Rationale for this study

The presented data clearly suggest the possibility of using solutions for peritoneal dialysis containing osmolar agents like xylitol and L-Carnitine. These solutions could not only significantly decrease the amount of glucose currently present in commercial PD solutions, but also to take advantage of the described metabolic properties of LC and xylitol, and to correct potential LC deficiency. A synergistic effect of the two componds in improving glucose and lipid homeostasis in PD patients may conceivably be anticipated. The xylitol-glucose-LC based PD solution is also characterized by a more biocompatible profile than glucose-based ones. It is anticipated that a PD solution with such osmolar agents added to glucose, used for the nocturnal exchange, will lead to a significant reduction of glucose level in peritoneal dialysis solution during the night dwell, while preserving or even improving the depurative efficacy of the standard PD solution containing glucose 2.5%. The reduction of glucose level could be further enhanced if the PD solution with xylitol and carnitine will be used for the diurnal exchanges and a PD solution with icodextrin will substitute the standard PD solution containing glucose 2.5% for the nocturnal dwell.

3 STUDY OBJECTIVES

The aim of this study is to compare

1) he effects of an experimental solution, named IPX15 ,containing glucose (0.5%), xylitol (1.5%) and L-carnitine (0.02%) as osmotic agents comparable to the standard 2.5% glucose PD solution, for the nocturnal exchange in 20 ESRD patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) (Group A)
   or
2) the effects of an experimental solution, named IPX07 , containing glucose (0.5 %) Xylitol (0.7 %) and L-Carnitine (0.02 %) as osmotic agents comparable to the standard 1.5 % glucose PD solution, for diurnal exchanges (1, 2 or 3 exchanges), combined with icodextrin for the nocturnal dwell, in 20 ESRD patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) (Group B)

3.1 Primary Objectives

1. To assess the safety and tolerability of the experimental solutions by:
   - recording the incidence and severity of adverse events;
   - recording a subjective questionnaire on the patient's perception of well being;
   - monitoring the changes in routine blood biochemical and hematological parameters.

3.2 Secondary Objectives

1. To assess the effects of experimental solutions
   - peritoneal clearances;
   - peritoneal transport characteristics with respect to Day 0 and the follow-up period
2. To assess the effects of experimental solutions on peritoneum functionality by evaluation of changes in CA 125 and protein levels in ultrafiltrate

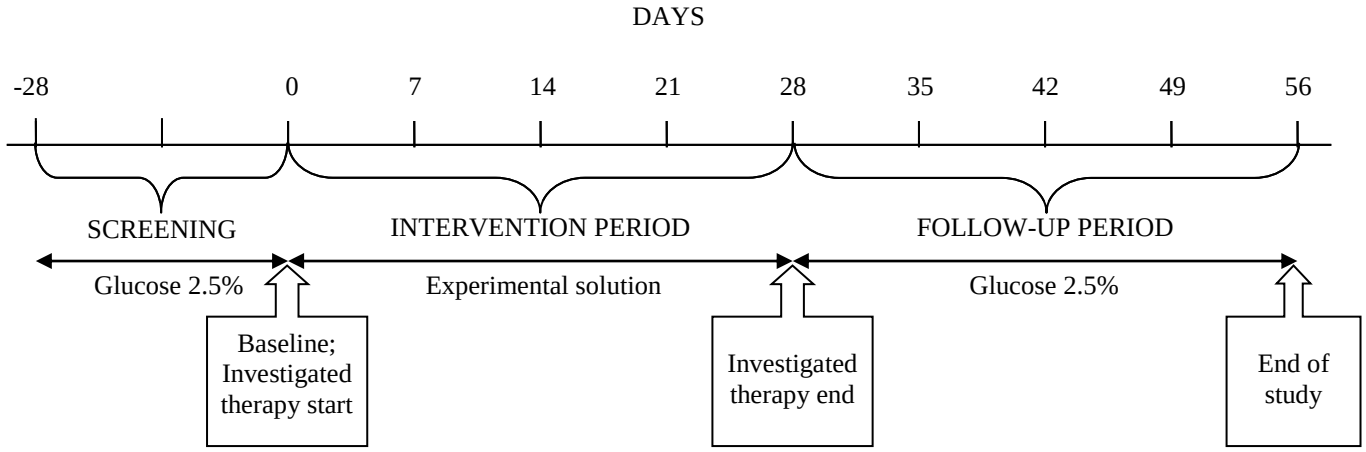
4 INVESTIGATIONAL PLAN

4.1 Study design

This is a phase II, prospective, investigational, open, multi-center study.

The study will consist of three study periods, with a total duration of around 84 days (**Figure 4**).

Group A



Group B

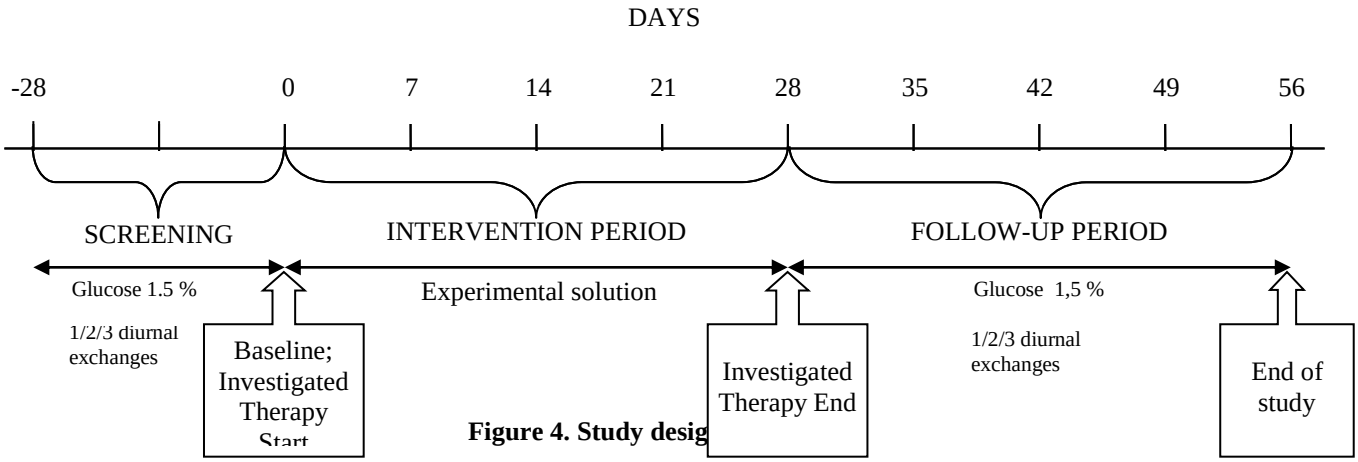


Figure 4. Study desig

4.2 Study plan

4.2.1 Screening period

The potential eligible patients will assign to Group A or Group B and enter a 4 weeks run-in period (screening period), dedicated to the identification of eligible subjects. It should comprise all clinical and laboratory assessments required to characterize the basal condition of patients in order to establish the accomplishment of inclusion criteria and the possible existence of exclusion criteria. The investigator should obtain, for every patient, a detailed medical/surgical history and perform an accurate physical examination, focusing on evaluation of concomitant diseases and prior or concomitant pharmacological therapies.

At the end of screening period (day 0), a careful analysis of eligibility should be performed: a subject could be enrolled only after a review of the laboratory results and after certifying that he matches inclusion and exclusion criteria.

During the screening period, Group A will receive standard solution with 2.5% glucose for the nocturnal exchange and Group B will receive their standard PD therapy (1,2 or 3 diurnal exchanges and one nocturnal exchange bag solution with icodextrin (Extraneal)) Before any study specific procedure is performed, the Investigator must request, obtain and document the written informed consent from all potential subjects in accordance with current available ethical guidelines: GCP and principles originated from the Declaration of Helsinki for medical research on human subjects. Eligible pre-menopausal female subject should sign a declaration that she agrees to use an efficient contraceptive method during the study period.

4.2.2 Intervention period

The intervention period will last for 4 weeks.
The subjects included in the Group A will receive a bag with experimental solution for the nocturnal dwell,
The subjects included in the Group B will receive 1, 2 or 3 bags with the experimental solution for the daily exchanges and a bag with icodextrin solution for the nocturnal dwell.
All subjects will come to the Center to undergo study visits. At each visit, the Investigator will perform clinical and laboratory assessments, according to the study flow chart. The patient compliance to treatment, changes in concomitant diseases and medications, and adverse events occurrence should be recorded..

4.2.3 Follow-up period

During a 4 weeks follow-up period, the subjects will return to the use of standard solution with 2.5% glucose for the nocturnal exchange (Group A) or of the solution with 1,5 % glucose for diurnal exchanges (Group B) and will come to the Center at days 42 and 56 to undergo study visits. On the occasion of these visits, the investigator will perform clinical and laboratory assessments, according to the study flow chart, in order to evaluate the potential changes in peritoneal membrane function consequently to the use of experimental solution.
The data regarding ultrafiltration volume, clinical parameters, concomitant medication, and occurrence of adverse events will be recorded by the subject in his diary and will be transcribed in the case report form by the investigator on the occasion of subsequent hospital visits .

4.2.4 Study end

For each subject, the study procedures will end with completion of the follow-up period (day 56). The end of the study for each site will be defined by the closure visit of the monitor.

4.3 Study outcome variables

4.3.1 Efficacy

Outcome variables will be:

- daily ultrafiltration volume from baseline (i.e. day 0) to day 28 and 56;
- peritoneal equilibrium test from baseline to day 28 and 56;
- weekly total urea Kt/V from baseline to day 28 and 56;
- weekly total creatinine clearance from baseline to day 28 and 56.

4.3.2 Safety and tolerability

Outcome variables for safety and tolerability assessment will be:

- incidence and severity of adverse events during the intervention and follow-up periods;
- changes in the subjective questionnaire on the patient's perception of well being at days 28 and 56 as compared to baseline.
- occurrence of abnormal laboratory values at days 14, 28 and 56 as compared to baseline.
- change in CA 125 and protein levels in ultrafiltrate from baseline to day 28 and 56.

The parameters for safety and tolerability assessment are detailed in **Section 8**.

4.4 Study flow chart

		SCREENING PERIOD		***INTERVENTION PERIOD***		***FOLLOW-UP PERIOD***	
Day		*-28*	*0*	*14*	*28*	*42*	*56*
Demographic data		✍					
Written informed consent		✍					
Medical and surgical history		✍					
Physical examination		✍					
Previous medication		✍					
Concomitant diseases		✍	✍	✍	✍	✍	✍
Concomitant medication		✍	✍	✍	✍	✍	✍
Clinical parameters[a)]		✍	✍	✍	✍	✍	✍
Pregnancy test		✍					
Eligibility criteria		✍	✍				
Functional parameters	Weekly urea KT/V		✍		✍		✍
	PET		✍		✍		✍
	Total creatinine clearance		✍		✍		✍
	Plasma		✍	✍	✍	✍	✍
Carnitine level	Urine		✍	✍	✍	✍	✍
	Dialysate		✍	✍	✍	✍	✍
Ultrafiltration	Nocturnal	✍	✍	✍	✍	✍	✍
	Total	✍	✍	✍	✍	✍	✍
Clinical chemistry [b)]		✍	✍	✍	✍	✍	✍
Hematology [c)]		✍	✍	✍	✍	✍	✍
Uric, lactic and oxalic acids		✍*	✍	✍	✍	✍	✍
Electrocardiogram (ECG)			✍		✍		
CA 125 / proteins in ultrafiltrate		✍	✍	✍	✍		✍
Bag accountability				✍	✍		
Adverse events				✍	✍	✍	✍
Subjective questionnaire			✍		✍		✍
End of study form							✍
Investigator's confirmation							✍

a) : Clinical parameters will include diuresis.

b): Clinical chemistry will consist of: serum sodium, potassium, , calcium, phosphorus, total protein, albumin, GOT (AST), GPT (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, fasting glucose, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, blood urea nitrogen (BUN), and creatinine;

c) : Hematology will consist of: hemoglobin, hematocrit, RBC count, WBC count and WBC differential, and platelet count;

✍*: At day -28, only uric acid determination will be performed;

5 SUBJECTS

5.1 Sample size

Because of the lack of available data regarding the effects of studied pharmacological association in ESRD patients undergoing CAPD, the calculation of sample size were done on the base of a subjective questionnaire on the patient's perception of well being

40 patients with ESRD treated by CAPD will be included 20 in Group A and 20 in Group B.

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P.IVA 01702360684

5.2 Target study population

Stable, End-Stage Renal Disease (ESRD) patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) without major cardiovascular comorbidities, regularly treated for at least three months before selection with a standard solution containing 2.5% of glucose for the nocturnal dwell (Group A) or regularly treated for at least one month before selction with 1; 2 or 3 diurnal exchange bag solution containing 1.5 % glucose combined with a nocturnal exchange with Extraneal, will be investigated.

5.3 Selection of the study population

5.3.1 Inclusion criteria

For inclusion in the study, patients of both genders must fulfill the following criteria, verified during the screening period:

1. Age ≥18 years;
2. Diagnosis of ESRD treated for at least three month with CAPD, as stated by the medical staff of the center;
3. Stable clinical condition within four weeks before screening period, certified by medical/surgical history, physical examination and laboratory exploration;
4. Hemoglobin level ≥9g/dL;
5. Absence of acute peritonitis and/or peritoneal catheter infection (either exit site or subcutaneous tunnel) episodes within three months before selection;
6. To understand and sign an informed consent form.

For patients who will be included in Group B, the following criteria must be fulfilled too:

7. Be treated with Extraneal (nocturnal exchange bag solution) for at least 1 month
8. Be treated with 1; 2 or 3 diurnal exchange bag solutions (solution bags with 1,5% glucose) and one nocturnal exchange bag solution with icodextrin (Extraneal).

5.3.2 Exclusion criteria

Patients who fulfill one or more of the following criteria will not be enrolled in the study:

1. History of alcohol or drug abuse in the last six months before selection for the study;
2. Androgen therapy in the last six months before selection;
3. Active infections;
4. History of congestive heart failure stage III and IV NYHA;
5. History of major cardiovascular events like stroke, acute myocardial infarction, coronary or other arterial revascularization procedures in the last three months before selection;
6. Clinically relevant cardiac arrhythmia;
7. Clinically relevant abnormalities of functional hepatic tests;
8. Therapy with L-carnitine or its derivatives in the last three months before selection;
9. Pregnancy, lactating women or female subjects of childbearing potential who do not use an effective method of contraception;
10. Presence of relevant chronic medical conditions that could suggest exclusion of patient from the study or could interfere with assessment of study parameters, especially if the life expectation is less then one year;
11. Participation in another clinical study within the past month;
12. Known allergic reactions to L-carnitine or xylitol.

5.3.3 Removal of subjects from the study

The investigator could remove a patient from the study (subject withdrawal) if any of the following situations occur:

1) Withdrawal of the subject's informed consent;
2) Initiation of a disallowed concomitant therapy;
3) Occurrence of an unexpected or serious/severe adverse event that could interfere with study evaluation or make its continuation inappropriate;
4) Changes of the subject's clinical condition that could interfere with study evaluation or make its continuation inappropriate;
5) Subject's non-compliance.

In any case of premature discontinuation from the study, the reason should be recorded in CRF as accurate as possible. In case of withdrawal due to a serious adverse event (SAE), the investigator should follow-up and registers the evolution of adverse event until its resolution.
In subjects withdrawn from the study, the investigator should make any reasonable effort to perform all the assessments scheduled for the last visit of the study in order to conclude on the investigated treatment.
The study will be discontinued in case of appearance of new information about the investigational product showing an augmentation of risk for the patient.

6 TREATMENT PROCEDURES

6.1 Treatment during the study

The experimental solution used in this study will be produced in accordance with Good Manufacturing Practice (GMP) by Haemopharm Biofluids s.r.l., Via dell'Industria - Tovo di Sant'Agata (SO) Italy, and will be provided to investigators free of charge.
The icodextrin solution bags required for the Group B will also be provided to Investigators free of charge by the Sponsor.
Two different experimental solution bags will be used (see 6.1.2 for composition).

- **Product code IPX15**: the formulation comprises bag with sterile solution for peritoneal dialysis containing glucose (0.5%), Xylitol (1.5%) and L-Carnitine (0.02%) to be used in the Group A treated with the experimental solution bag during the nocturnal exchange;
- **Product code IPX07**: the formulation comprises bag with sterile solution for peritoneal dialysis containing glucose (0.5%), Xylitol (0.7%) and L-Carnitine (0.02%) to be used in the Group B treated with the experimental solution bags during the 1, 2 or 3 diurnal exchanges

6.1.1 Dosage, schedule and administration of investigational product

During the 4-weeks Intervention Period patients will be treated according the following schedule:
GROUP A: the bag with experimental solution (product code IPX15) will be used for the nocturnal exchange;
GROUP B: the bag with experimental solution (product code IPX07) will be used for the diurnal exchanges (1; 2 or 3), while a bag with icodextrin solution will be used for the nocturnal exchange.

6.1.2 Composition of the investigational product

The two different sterile experimental solution bags for peritoneal dialysis have the following composition:

Active compounds		
	IPX15	IPX07
L-carnitine (%)	0.02	0.02
Xylitol (%)	1.5	0.7
Glucose (%)	0.5	0.5

Eccipients		
	IPX15	IPX07
Sodium (*mmol/L*)	134	134
Calcium (*mmol/L*)	1.75	1.75
Magnesium (*mmol/L*)	0.5	0.5
Chloride (*mmol/L*)	103.5	103.5
L-lactate (*mmol/L*)	35	35
pH	5.5	5.5

6.1.3 Producing and labeling

Galenica Senese Srl will perform the manufacturing and labeling of experimental solution bags in accordance with current legislation: each solution bag will be identified by a batch number, expiration date, and also by information reported on the labels according to current legislation. The bags must be stored at temperature between 4°C and 25°C, protected from light, in a secure, lockable place with limited access only for persons involved in the study.

Solution bags will be provided to each subject as 4-bags packaging including PVC empty bag. It must be used the MINISET transfer set for peritoneal dialysis, with Luer-Lock connection, consistent with Twin-Bag Baxter and with Set Home Choice Baxter.
The experimental solution bag will be identified as follow.

Product code IPX15
Each solution bag will be identified by a label with the following information:

Sponsor: **Iperboreal Pharma S.r.l.** Via Piave, 110/7 65122 Pescara (CH) Italy Ph + 39-085-2034834	Prodotta da **Galenica Senese s.r.l.** Via Cassia Nord, 351 53014 Monteroni d'Arbia (SI) Italy
Contents: solution bag for peritoneal dialysis contaning glucose (0.5%), Xylitol (1.5%) and L-Carnitine (0.02%) **Dosage**: 1 bag for nocturnal exchanges intraperitoneal route **Batch** no: ……..... **Expiry Date**: ..... **Protocol IP-001-09** **Subject No._____** **For investigational use only** **Store at a temperature between 4° C and 30 °C** **Keep out of children**	

Each package will be identified by a label with the following information:

Sponsor:	Prodotta da
Iperboreal Pharma S.r.l. Via Piave, 110/7 65122 Pescara (CH) Italy Ph + 39-085-2034834	**Galenica Senese s.r.l.** Via Cassia Nord, 351 53014 Monteroni d'Arbia (SI) Italy

Contents: 4 disposable sterile solution bags for peritoneal dialysis containg glucose (0.5%), Xylitol (1.5%) and L-Carnitine (0.02.%) and proper dwillig empty bag
Dosage: 1 bag for nocturnal exchanges intraperitoneal route
Batch No …… Expire Date …….

Protocol IP-001-09
Subject no _____
Investigator: **XXXXX XXXXX**
Address: **XXXXX XXXXX**
For investigational use only
Store at a temperature between 4° C and 30 °C
Keep out of children

Product code IPX07
Each solution bag will be identified by a label with the following information:

Sponsor:	Prodotta da
Iperboreal Pharma S.r.l. Via Piave, 110/7 65122 Pescara (CH) Italy Ph + 039-085-2034834	**Galenica Senese s.r.l.** Via Cassia Nord, 351 53014 Monteroni d'Arbia (SI) Italy

Contents: solution bag for peritoneal dialysis contaning glucose (0.5%), Xylitol (0.7%) and L-Carnitine (0.02%)
Dosage: 1; 2 or 3 bags for diurnal exchanges intraperitoneal route
Batch no: ……..... **Expiry Date**: .....

Protocol IP-001-09
Subject no._____
For investigational use only
Store at a temperature between 4° C and 30 °C
Keep out of children

Each package will be identified by a label with the following information:

Sponsor:	Prodotta da
Iperboreal Pharma S.r.l. Via Piave, 110/7 65122 Pescara (CH) Italy Ph + 39-085-2034834	**Galenica Senese s.r.l.** Via Cassia Nord, 351 53014 Monteroni d'Arbia (SI) Italy

Contents: 4 disposable sterile solution bags for peritoneal dialysis containg glucose (0.5%), Xylitol (0.7%) and L-Carnitine (0.02.%) and proper dwillig empty bag
Dosage: 1; 2 or 3 bags for diurnal exchanges intraperitoneal route
Batch No …… Expire Date …….

Protocol IP-001-09
Subject no _____
Investigator: **XXXXX XXXXX**
Address: **XXXXX XXXXX**
For investigational use only
Store at a temperature between 4° C and 30 °C
Keep out of children

6.1.4 Accountability

A qualified courier will deliver the IMP directly to patients' home, upon request by the deputed investigator by means of the IMP Accountability Form.
The Pharmacist and/or the Principal Investigator will be responsible for the receipt, adequate storage, handling and use of the dialysis solution in the study.
The partially used or unused dialysis solution bags should be retrieved by the courier after the study termination.
Patients will be not obliged to return to Investigators the empty drain bags, except if a Serious Adverse Event onset in abdominal apparatus (i.e. peritonitis).
The patient will keep the evidence of received and used bags with experimental solution in his regular Peritoneal Dialysis Diary (see Compliance section 6.3), and this will serve as additional documentation for completion of the inventory.

6.2 Concomitant pharmacological therapy

The information regarding concomitant pharmacological treatment comprise data concerning the drugs regularly received during the last three months before enrollment (recorded in section "**Previous Medication**" from CRF) and data concerning therapies received in the moment of inclusion into the study (recorded in section "**Concomitant Medication**" from CRF).
Any pharmacological therapy administered for pathology unrelated to the study, considered necessary for the patient's well being and that does not interfere with the investigational product, may be given at the discretion of the investigator or personal physician of the patient. All these drugs must be recorded in the appropriate section of CRF, noting the dosage, date and duration of administration in correlation with indication.
If after starting the intervention period of the study with experimental solution the administration of another drug becomes necessary for any symptom/sign, this therapy has to be reported in section "**Concomitant medication**" from CRF.
Changes in dosage of any concomitant medications decided by the investigator must be recorded in the original files of the medical institution where the patient is treated (hospitalization files, dialysis files or similar) and in the CRF.

6.2.1 Allowed concomitant pharmacological therapy

Concomitant therapy with the following drug categories will be allowed:

- anti-hypertensives, coronary vasodilatators, tonicardiac drugs;
- aspirin, antithrombotic drugs and coumarins anticoagulants;
- erythropoiesis-stimulating agents, intravenous iron;
- contraceptives.
- any drug considered necessary for pathology unrelated to the study, as judged by the investigator or personal physician of the patient, that does not interfere with the investigational product.

The therapeutic regimen of ESRD patients on CAPD is considered stable if the dosage of any of the drugs used has not been modified in relation to the follow-up of the laboratory parameter values. Therefore, the term "therapeutic stability" refers rather to the stability of the patient's clinical status then to the absence of dosing changes. Hence, the dose adjustment of any drug required for the treatment of studied pathology is not o reason for non-inclusion of a patient in the study or for his premature discontinuation. These changes should also be recorded in the Case Report Form of the subject.

Those patients who start or interrupt administration of a drug during the last month before screening could not be included in the study.

6.2.2 Disallowed pharmacological therapy

If the patient was treated with L-carnitine or a derivative, these drugs must be stoped with at least three month before selection for the study. The change of the dialysis bag for the nocturnal exchange is disallowed during the entire study period.

6.3 Compliance

The investigator must explain to patient the importance of regularly use of the bag with experimental solutions l and the patient must keep an accurate evidence of its use in his regular Peritoneal Dialysis Diary.
The investigator should record in the corresponding section of the CRF the observations on prescription and the calculation of compliance to treatment.
The assessment of compliance to treatment, defined as the patient's adhesion to the prescribed dosage (ratio between the number of bags actually used and the number of bags that should be used), will be performed at the end of the study. The assessment of compliance to treatment will be used for the statistical evaluation of results, patients being considered:

- compliant (adherent) – patients who have used at least 80% of the bags with experimental solution;
- non-compliant (non-adherent) – patients who have used less then 80% of the bags with experimental solution.

6.4 Discontinuation of the experimental solution usage

The use of experimental solution may be withholded and/or stoped by the patient at any time he wish or by the investigator when he considers appropriate according to the subject's clinical condition. The investigator must completely document any interruption and/or stop of the experimental solution use in the CRF.
The experimental treatment may be prematurely withholded and/or stoped for the following reasons:

A. withdrawal of the patient's consent;
B. occurrence of an adverse event, which could interfere with the patient's evaluation and would render the continuation of the study inappropriate;
C. logistical changes that would render impossible the patient's participation to the planned study visits according to the study flow chart.

For each patient who withhold and/or stop the investigated treatment, the complete final assessement as scheduled for the end-of-study visit should be performed, if possible, and the results should be recorded in the Case Report Form (CRF), together with the reason of discontinuation.
It will be the investigator responsability to follow-up the patient for an adequate period (30 days) in order to evaluate the clinical condition, to perform a laboratory examination and to survey possible occurrence of adverse events even at distance after the cessation of experimental treatment.
It is also recommended for these patients to fulfill the follow-up period in accordance with the study protocol after they will be taken into account for the safety and tolerability analysis.

7 EFFICACY ASSESSMENT

7.1 Efficacy parameters

Since the study has an explorative character, no primary and secondary efficacy parameters were identified. The following efficacy parameters will be assessed during the study:

1. Peritoneal Equilibrium Test (PET);
2. weekly total urea Kt/V (KT/V);

3. weekly total creatinine clearance (CrCL);
4. ultrafiltration (UF);

	SCREENING PERIOD		***INTERVENTION PERIOD***		***FOLLOW-UP PERIOD***	
Day	*-28*	*0*	*14*	*28*	*42*	*56*
Weekly total urea Kt/V		☒		☒		☒
PET		☒		☒		☒
Weekly total creatinine clearance		☒		☒		☒
Total ultrafiltration	☒	☒	☒	☒	☒	☒
Nocturnal ultrafiltration	☒	☒	☒	☒	☒	☒

PET, KT/V, CrCL and UF will be performed according to the standard clinical procedure

7.2 Carnitine absorption, distribution and metabolism

Measuring the free carnitine and its acyl-derivatives levels in blood, urine and peritoneal effluent will assess the absorption, distribution and metabolism of the carnitine.

Moments for analysis

In the last day of the Screening Period (day 0), a venous blood sample (5 mL) will be drawn in the morning, after nocturnal dwell, concomitantly with a peritoneal effluent sample (10mL) and an urine sample (10mL) from the 24-hour urine collection, for the assessment of basal levels of total carnitine (TC), free carnitine (FC) and acetyl-carnitine (AC).
At the next nocturnal exchange (Intervention Period day 1), the patient will begin the administration of the first experimental solution containing glucose, xylitol and carnitine.
The absorption, distribution and metabolism of L-carnitine will be evaluated from the following examinations:

Blood samples **(5 mL of blood)**	*Day* *0, 14, 28, 42, 56*	at the end of the nocturnal dwell after the peritoneum was emptied
Dialysate samples	*Day* *0, 14, 28, 42, 56*	A sample of peritoneal dialysate (10 mL) will be collected from the effluent obtained after nocturnal dwell
Urine samples	*Day* *0, 14, 28, 42, 56*	A sample of urine (10 mL) from the 24-hour urine collected during the day before hospital visit will be analyzed

The blood sample will be centrifuged at 1200g for 10 minutes and the plasma aliquot will be used for carnitine levels determination (90).
The plasma, urine and peritoneal effluent samples will be stored -20°C and transported on dry ice to Central Laboratory in charge of the determination.
The samples will be analyzed by Biochemistry and Molecular Biology Operation (UOC) lab, Policlinico A. Gemelli (Largo Agostino Gemelli 8, 00168 Roma) The material of use (provided free of charge by Sponsor) and the methodological procedures will be described in a document specially prepared for the study.
Laboratory Responsible (Dott. Andrea Urbani) will provide the normal range for each analyte, the description of the equipment and certifications relating to validation and quality assurance controls.

8 SAFETY AND TOLERABILITY ASSESSMENT

8.1 Safety and tolerability parameters

Since few adverse events were found after L-carnitine administration in humans and none severe adverse event was reported, it seems that L-Carnitine is well tolerated. A list with all previous adverse events observed during the administration of LC is included in the Investigator's Brochure of the experimental product.
Also, xylitol is well tolerated by human organism as demonstrated by its utilization as substitutive sugar instead of glucose during parenteral nutrition (in dose of 3g/kg/day). The only known disadvantage of intraperitoneal substitution of glucose with xylitol is the increase of uric and lactic acid production, but with the enhanced values still within normal ranges. These effects occur only for dosage higher then 150g/day, when other adverse events as nausea, vomiting, increased levels of bilirubin and serum transaminases were observed as well.
The safety and tolerability of the studied product will be assessed at the end of the study by analyzing some clinical and biochemical data recorded for each enrolled subject. The main informations will be derived from subject's demographic data, medical history, physical examination, clinical parameters, concomitant diseases and therapies (allowed by the study protocol), ECG, laboratory data, adverse events occurrence and data regarding discontinuation from the study. All these informations will be recorded in the appropriate sections of the CRF.
The following procedures will be performed for assessing the safety and tolerability.

8.1.1 Medical/surgical history

The investigator should obtain an accurate medical/surgical history during the screening period (day -28), including details regarding the pathology from last year before the study selection. Also, data about previous medications should be carefully registered, focusing on the last three months before the study.
The concomitant diseases and concomitant pharmacological therapies should be recorded at the first visit from the screening period (day -28). All changes occurred during the study periods will be recorded as variations in the clinical status of the subject (as adverse events or changes in concomitant medications).

	SCREENING PERIOD		***INTERVENTION PERIOD***		***FOLLOW-UP PERIOD***	
Day	*-28*	*0*	*14*	*28*	*42*	*56*
Medical/surgical history	✍					
Previous medication	✍					
Concomitant diseases	✍	✍	✍	✍	✍	✍
Concomitant medication	✍	✍	✍	✍	✍	✍

8.1.2 Physical examination

A complete physical examination will be performed by the investigator at the site (local dialysis center) during the screening period (day -28). Any clinical relevant abnormality of any system or organ must be recorded in the appropriate section of the CRF.

	SCREENING PERIOD		***INTERVENTION PERIOD***		***FOLLOW-UP PERIOD***	
Day	*-28*	*0*	*14*	*28*	*42*	*56*
Physical examination	✍					
Subjective questionnaire		✍		✍		✍

A supplimentary assessment of tolerability will consist in a subjective questionnaire on the patient's perception of well being (**Appendix I**) that should be administered at baseline, day 28 and day 56 and will be completed by the subject himself.

8.1.3 Clinical parameters

The clinical parameters, including height (only at day -28 from the screening period), weight, arterial blood pressure, heart rate, diuresis (L/day) and hyperhydration signs will be recorded by the investigator at the site (local dialysis center) at all the study visits, according to the following schema:

	SCREENING PERIOD		***INTERVENTION PERIOD***		***FOLLOW-UP PERIOD***	
Day	*-28*	*0*	*14*	*28*	*42*	*56*
Clinical parameters	✍	✍	✍	✍	✍	✍

8.1.4 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at the site (local dialysis center) at the end of the Screening Period and at the end of the Intervention Period:

	SCREENING PERIOD		***INTERVENTION PERIOD***		***FOLLOW-UP PERIOD***	
Day	*-28*	*0*	*14*	*28*	*42*	*56*
Electrocardiogram		✍		✍		

8.1.5 Uric, lactic and oxalic acids determination

The uric acid, lactic acid and oxalic acid will de measured in order to evaluate the tolerability of experimental solution relative to these laboratory parameters.
The determinations will be scheduled according to the study flow chart, as follows:

	SCREENING PERIOD		***INTERVENTION PERIOD***		***FOLLOW-UP PERIOD***	
Day	*-28*	*0*	*14*	*28*	*42*	*56*
Uric acid	✍	✍	✍	✍	✍	✍
Lactic acid		✍	✍	✍	✍	✍
Oxalic acid		✍	✍	✍	✍	✍

The uric, lactic acid measurements will be performed locally, whereas the oxalic acid measurements will be ed tothe Extracellular Matrix Pathobiology laboratory, Department of Biomedical Sciences, University of Padova (via U. Bassi 58b, Padova).

The blood samples for uric acids measurements should be drawn under fasted conditions in the morning.

Laboratory Responsible (Prof. Maruzio Onisto) will provide the normal range for each analyte, the description of the equipment and certifications relating to validation and quality assurance controls

8.1.6 Other laboratory parameters

The patient's tolerability to treatment will be evaluated by measurements of the main laboratory parameters from drawn blood samples, in order to assess the safety and tolerability of the experimental solution used in this study.

	SCREENING PERIOD		***INTERVENTION PERIOD***		***FOLLOW-UP PERIOD***	
Day	*-28*	*0*	*14*	*28*	*42*	*56*
Clinical chemistry	✓	✓	✓	✓	✓	✓
Hematology	✓	✓	✓	✓	✓	✓
CA 125 / proteins in ultrafiltrate	✓	✓	✓	✓		✓

The following parameters will be measured:

- **Clinical chemistry**: serum sodium, potassium, , calcium, phosphorus, total protein, albumin, GOT (AST), GPT (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, fasting glucose, total cholesterol, HDL-cholesterol,
  LDL-cholesterol triglycerides, blood urea nitrogen (BUN), creatinine, C-Reactive Protein (CRP);
- **Haematology**: hemoglobin, hematocrit, RBC count, reticulocytes, WBC count and WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count;
- **CA 125 and protein levels** in the peritoneal effluent after the nocturnal exchange.
  In the following table is presented the timing of these laboratory examination performing.

Blood samples will be drawn in the morning, after at least 8 hours of fasting.
All the assessments will be performed locally . The results will be expressed in Standard International Units or in conventional units.

Laboratory Responsible will provide the normal range for each analyte, the description of the equipment and certifications relating to validation and quality assurance controls

CA 125 and proteins in the ultrafiltrate

CA 125, a glycoprotein with high molecular weight, is considered as a marker of the mesothelial cells mass. In dialysis patients, CA 125 is normal, but the high concentration in peritoneal effluent suggests a local release of mesothelial cells. A decrease of CA 125 level in peritoneal effluent over time indicates the loss of mesothelial cells, thus CA 125 being a *in vivo* marker of peritoneal solution biocompatibility.
The loss of proteins in the ultrafiltrate (peritoneal effluent) will be used as marker of the experimental solution tolerability.
The effluent dialysis solution samples (5 mL), for CA 125 and protein levels in the peritoneal effluent after the nocturnal exchange measurements, will be collected in labeled plastic tubes for transportation, will be stored at –20°C until expedition, on dry ice, to the Central Laboratory in charge of the determination.
The samples will be analyzed locally.

Relevant laboratory abnormalities

The investigator should verify, interpret and record in CRF the laboratory results, indicating the abnormal values by a code for clinical relevance. Any abnormal value that is considered clinically relevant (not explained by the previous known subject's diseases) should be reported as adverse event in the appropriate CRF section. In this case, the laboratory test should be repeated immediately and periodically thereafter until the value's normalization, establishing an adequate explanation for the variation or the demonstration of its stabilization.
All these data and explanations should be recorded in the Adverse event section of the CRF.

8.1.7 Adverse events

The clinical tolerability of the investigational product will be evaluated by registration of adverse events or adverse reactions described by the patient or observed by the investigator. All these

adverse events occurred during the study period must be recorded in the appropriate section of the CRF.

Definitions

a) Adverse Event

The Adverse Event (AE) is defined as *any untoward medical occurrence in a patient or clinical investigation subject who received a pharmaceutical product and which does not necessarily have a causal relationship with this treatment*. An adverse event can be any unfavorable and undesirable medical condition: sign (including an abnormal laboratory finding), symptom or disease (including the worsening of a pre-existing medical condition) temporally associated with the use of a medicinal product, **whether or not considered causally related** to the medicinal product.

b) Adverse reaction to the drug (ARD)

Adverse reaction (side effect) is defined as *any noxious and unintended response to a medicinal product related to the normal dosage used in humans for prophylactic, diagnostic or therapeutic purposes or for changing a physiological function*. The phrase "response to a medicinal product" means that a causal relationship between the medicinal product and the adverse event is at least reasonable possible, i.e. the **relationship cannot be ruled out**. Therefore, those reactions that "doubtfully" correlate with the investigated medicinal product should be considered side effects as well as those for which there are not indications for establishing correlation at the moment of its appearance.

c) Unexpected Adverse Event/Reaction

An unexpected adverse reaction is the adverse reaction that was not mentioned in the informative materials regarding the investigated product *(for example: Investigator's Brochure for a product in experimental period; abstract of the product's characteristics for a product already on market)*.

Classification

Adverse events are classified in "Serious" and "Non Serious".

Serious Adverse Event or Serious Adverse Reaction

A Serious Adverse Event or Reaction/Experience is an adverse event that fulfils one or more of the following criteria:

A. results in patient's death;
B. is immediately life-threatening;
C. requires in-patient hospitalization or prolongation of existing hospitalization;
D. results in persisting or significant disability or incapacity;
E. *is a congenital abnormality or birth defect*:
F. *Other medical condition with significant hazard according to the investigator's opinion*.

Medical and scientific judgment should be exercised in deciding whether the urgent notification is appropriate in other medical conditions, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above. *These events should usually be considered serious*.

Should be included among serious adverse events also those reactions that occur consequently to the use of medicinal product without conformity with the abstract of product's characteristics (for example an overdose or abuse of the medicinal product).

The term "serious" should be distinguish from the term "severe":

A. the term "severe" (or relevant) describes the intensity of an event (like mild, moderate or severe myocardial infarction) and such an event may be of minor medical relevance (like a severe headache);
B. the term "serious" is based on its outcome and is defined by the patient's exposure to major risks, inclusive life-threatening (see above). The seriousness of an event defines the obligation of notifying the Legal Authorities. This type of adverse reactions must be immediately reported

to the Legal Authorities as specified in the current accepted guidelines.

C.

Non-serious Adverse Event

The Non-serious Adverse Event is the adverse event that does not meet the criteria for serious adverse event definition.

Recording of Adverse Events

All investigators involved in the study must complete the standard section for obtaining information related to adverse events, which is inserted in the CRF. All AEs must be documented in the appropriate section of the CRF.

Reporting procedures for Serious Adverse Events

In case of a Serious Adverse Event, the investigator must additionally document all related data from AE section in CRF to the **SERIOUS ADVERSE EVENT REPORT FORM**, consisting of 3 pages and containing a detailed description of the event and its outcome. This form, together with a completed expedition form, must be sent by fax within 24 hours of discovery or notification of event to:

Sequre S.r.l. E-mail.: safety@sequrelifesciences.com

Fax: +39 0656561998

Sequre staff will request additional information, if necessary for the evaluation of SAE. In response, the investigator must send a completed **SAE QUERY FORM**. When necessary, accompanying medical documents (i.e. copies of hospital or autopsy reports) and relevant pages from CRF should also be sent. The SAE form must be sent together with a transmission file (FILE FOR SAE FORM TRANSMISSION) that contain the name of investigator and its contact address (fax, phone, e-mail) and will be provided with the Investigator's File.

Reporting procedures for non-serious adverse events

Non-serious adverse events will be identified at all study visits and will be recorded in the appropriate section of CRF, each event on a separate page. A brief description of the event with: dates of onset and resolution, intensity degrees, frequency of occurrence, treatment required, studied product action taken, outcome, causality/relationship with investigational product and whether the event is classified as serious must be provided.

The intensity of AE must be assessed and recorded in the CRF as follows:

- mild: an AE that does not interfere with usual activities.
- moderate: an AE that interferes with usual activities.
- severe: an AE that is intense or debilitating and interferes with usual activities.

The investigator will assess the causality/relationship between the investigational product and the AE, using the following categories:

- definitely related;
- probably related;
- possibly related;
- unlikely related;
- not related.

The completed AE page will be take by the study monitor the first monitoring visit after the end of AE and will be give to the responsible person with study Data-base.

When, during the study, a non-serious adverse event has an unfavorable evolution toward serious adverse event in the investigator's opinion, the recommended procedures for this category must be followed.

9 DIRECT ACCESS TO THE ORIGINAL FILES

The investigator must allow the direct access of all authorised representatives of regulatory national and international authority, Independent Ethics Committee, and of the study initiator to the all original documents of the study (including signed subject's Informed Consent form, study files, study protocol, Case Report Forms, source data files – original medical records/files like hospital or ambulatory registries, patient's Peritoneal Dialysis Diary). For those documents that can not be kept in original at the study site (for example, the patient's Peritoneal Dialysis Diary), a photocopy authenticated by the investigator under signature as being in conformity with the original can replace it.
All subject's data from these files shall be treated confidentially, in accordance with legal procedures.

10 PROCEDURES FOR QUALITY CONTROL

The organization, monitoring and quality assurance of the present study will be the responsibility of Iperboreal Pharma S.r.l.

10.1 Case Report Form

The Case Report Form (CRF) is the document designed for recording all the information required by the protocol on each subject taking part in the study and which is to be reported to the Sponsor. The information required by the CRF copies the information layout required by the protocol for each subject selected and taking part in the research.
The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in this document. Data deriving from source documents should always be consistent with the source documents, or the discrepancies should be explained.
The CRF to be used in this study consists of specific pages for any of the information required by the protocol (e.g., Informed Consent, eligibility, efficacy and safety assessments, Adverse Events recording, study termination/discontinuation, etc.).
How to use the CRF
For this trial a standard electronic data capture solution with electronic case report forms (eCRF) will be used. All data are collected and documented in the web-based application ACTide (Nubilaria) delivered by Sintesi Research in Milano.
The electronic CRFs are used to record study data and are an integral part of the study and subsequent reports.
Each patient will be given a specific patient number.
The system keeps a full audit trail of the data values, date and time of modification, and the electronic signature of the user who performed the change.

10.1.1 Identification of original documents

The demographic data, medical history information, physical exam including clinical parameters (arterial blood pressure, heart rate, height, weight, diuresis), and data regarding peritoneal dialysis (timing, used bags, instilled volume, peritoneal effluent volume and aspect) should be registered in the Peritoneal Dialysis Patient' file on the local dialysis center. This file will be the main source document. Other source documents could be the patient's Peritoneal Dialysis Diary and the written results of laboratory analysis.

10.2 Clinical monitoring

The clinical monitoring activity will be assured by Iperboreal Pharma S.r.l. trough a specialized company (Sintesi Research S.r.l.), which will assume the activity as stipulated in the contract, in accordance with the ICH Note for Guidance on Good Clinical Practice in European Union.

The aim of monitoring is to certify the accuracy of study procedure completion through maintaining contact by phone and visits with the coordinating investigator and his staff.
At the start of the study, the monitor will do an Initiation Visit to the site in order to clarify with the involved staff the study protocol, the modality of collecting study data and completion of the study documents, especially the informed consent form, and the modality of handling the investigational product and study documents. During the study, the Periodical Monitoring Visits will verify the adherence to study protocol, check the study progress, and identify and solve any problem that could arise during its execution. At the end of study (The Final Visit) will be review the final report and the issues related to archiving the study documents.
With the occasion of these visits, the monitor should revise the source hospital and ambulatory files and the correctness of data reported in the CRF. Also, he should inform the study initiator about the study development.
Finally, the monitor should provide to investigators all needed study materials and should confirm to the study initiator that the study is conducted according to the protocol as concerns both data's registration and experimental procedures.

10.3 Audits

The investigator must allow the study initiator to perform audits as a part of quality assurance. The audit is an independent control of study-related activities and documents, distinct from monitoring, with the purpose to ascertain that these activities are conducted and data are recorded, analyzed and transmitted according to the protocol, GCP and all applicable regulatory requirements.

10.4 Inspections

The investigator and experimental institution must allow the national/international regulatory authorities to perform inspections.
The inspection from a regulatory authority consist of an official examination of the documents, structure, registrations and any other resource considered in relation with the clinical study by the authority.

11 DATA MANAGEMENT

The Source Data verification will be through the following steps:

- The monitor ensures the correct and complete entry of the experimental data in the eCRF and verifies their correspondence to the Source Document at the Investiagtional Site
- At the end of the investigation, the Data Manager will deal with the investigation data collected by arranging them in tables for subsequent statistical analysis

12 STATISTICS

12.1 Sample Size Calculation

The sample size has been calculated on the base of the following hypothesis about a subjective questionnaire on the patient's perception of well being
The null hypothesis (H0) presuppose that the state of health measured at the end of both treatments (experimental (day 28) and standard treatment (day 56)) remains unchanged, whereas the alternative hypothesis (H1) presupposes an improvement in the state of health at the end of the experimental treatment of at least one point within the 1 to 5 scale.

Given Δ=1, α, β equal to 0.05 and 0.20 respectively, with a standard deviation of the difference Δ equal to 1.5, at least 40 patients (20 Group A + 20 Group B) will be enrolled so that 80 treatments

(40 for Group) will be administered (each patient will be in fact treated first with the experimental treatment and then with the standard treatment)

12.2 General Considerations

All scores and quantitative variables will be tested for normality by means of the one-sample Kolmogorov-Smirnov test. Descriptives will be reported as mean±standard deviation or as median and interquartile range when appropriate. Counts and percentages will be used for categorical data. The Type I error will be set at 0.05. The following analyses presuppose the absence of a carry-over effect.

12.2.1 Efficacy Analysis

All efficacy analyses have an explorative character, so, for each analysis, the type I error will be set to the nominal level of 0.05.
Efficacy analysis will compare the effect of the "experimental solution" as osmotic agents with the standard PD solution for the nocturnal exchange.
As a first analysis, for all outcome variables (Peritoneal Equilibrium Test; weekly total urea fKt/V; weekly total creatinine clearance; ultrafiltration) values will be compared between the intervention period (from day 0 to day 28) and the follow-up period (from day 28 to day 56) by repeated measures analysis of variance with time and period as nested within factors.
As a second analysis, deltas will be computed between day 28 and day 0, relatively to the intervention period, and between day 56 and day 0, relatively to the follow-up period. For each evaluated period a one-sample t-test will be performed to test differences from zero of the delta variables. For each variable, deltas will be then compared between the two periods with a paired t-test or with a Wilcoxon test in order to study if changes from baseline after the use of the two solutions (experimental or standard glucose PD solution) are different.

12.2.2 Safety analysis

All patients who use at least one bag with the experimental solution or with the standard solution will be included in the safety analysis. Safety analyses will include tabulation of type and frequency of adverse events. Any serious adverse event will be reported with a comprehensive description.
Between-period differences in the proportion of adverse events will be analysed using Fisher's exact test whereas all continuous safety laboratory evaluations will be summarized using descriptive statistics, and deltas will be computed as differences between day 28-measurements and day 0-measurements as well as between day 56-measurements and day 0-measurements. In each evaluation period deltas will be analyzed by means of a one-sample t-test to test for possible changes from baseline, whereas possible differences between changes occurred in the experimental and follow-up periods will be analyzed by means of a paired t-test or by a Wilcoxon test according to the distributional normality of the considered variables. Occurrences of abnormal laboratory values at days 14, 28 and 56 will be tabulated and compared with those recorderd at baseline by means of a Fisher's exact test.

13 ETHICAL ASPECTS

All involved participants to this study will agree and assure that all experimental procedures will be performed in accordance with ethical principles, which have their origin in the Declaration of Helsinki (**Appendix II**) and are consistent with ICH/Good Clinical Practice guidelines and applicable regulatory requirements.

13.1 Ethics review

The investigator/experimental site shall be responsible for asking and obtaining the written approval of this study protocol by the local Independent Ethics Committee (IEC) before enrolment of any subject in the study. The investigator will provide to IEC all requested documents for this approval. The investigator must send a copy of the written approval to the medical responsible of the study initiator before the commencement of experimental procedures.
This study will be performed in accordance with the approval of the Medical Authorities and with the applicable regulatory requirements and laws.

13.2 Informed consent

Before study initiation, a form of the written informed consent of the patient and/or legally acceptable representative should be submitted to the Independent Ethics Committee and approved by this authority.
The informed consent form should be prepared in the language of the potential subject population.
The written informed consent must be asked, obtained and documented by the investigator in accordance with the applicable regulatory requirements, GCP guidelines and the principles from Declaration of Helsinki, after adequate explanation of aims, methods, anticipated benefits and potential hazards of the study.
Details regarding the procedure of asking and obtaining the informed consent are presented in ICH-GCP E6, paragraphs 4.3.3, 4.3.4, 4.8.2, 4.8.3, 4.8.4, 4.8.5, 4.8.6, 4.8.7, 4.8.8, 4.8.11, 8.3.2, 8.3.11, and paragraphs 4.8.9, 4.8.12, 4.8.13, 4.8.14, 4.8.15 for this procedure in special situations, respectively.
The subject's signed and dated informed consent must be obtained before any study-specific procedure, including the screening visit. The investigator must keep an exemplar of the signed informed consent form in the Investigator's file, and must give an exemplar to the patient.

14 ADMINISTRATIVE PROCEDURES

14.1 Changes to the study protocol or to the planned analysis

Any change to the study protocol that occurs after the final approval from the study initiator and study head investigator is designed as "Protocol Amendment". These amendments consist of changes in a document with legal value and therefore must be completed in duplicate and must be approved by the regulatory authorities. All protocol amendments should be submitted and approved by the ethical committee that already approved the study protocol, prior to their implementation. The study initiator will be responsible for this submission and approval obtainment.
The written approval of amendments will follow the same distribution and storage modalities as stated for the study protocol.
In case of changes concerning only administrative or technical aspects of the experimental procedures, the amendment will be recorded in a document entitled "Administrative change to study protocol" and will be simple send to the IEC as notification.
If the amendment has a major influence on the study design and on the potential hazards for the patient, every subject must be properly informed and must give in writing his agreement for continuation of the study. A new informed consent form will be prepared in accordance with the amendment by the study initiator or by the investigator and will be submitted for approval to the Independent Ethics Committee.

14.2 Study discontinuation

14.2.1 Whole study discontinuation

The study initiator may decide the discontinuation/interruption of the study if:

A. new data concerning the toxicological, pharmacological or clinical characteristics will render the study objectives or design unacceptable;
B. the rate of subject's recruitment will be ineffective;
C. the experimental site will not comply with the protocol requirements, especially in respect to inclusion/exclusion criteria;
D. the experimental site will not be able to comply with the requirements of the Good Clinical Practice (GCP Consolidated Guidelines CPMP/ICH/135//1995).

In these cases, the study initiator should promptly inform the investigator/experimental site and the Regulatory Authority of the premature discontinuation of the study, providing the reason for this discontinuation.
The investigator should also notify patients and the local Ethics Committee of the institution where the experimental site operates, explaining the reason for study discontinuation.

14.2.2 Study discontinuation by the Ethic Committee

The study may be discontinued also by the Ethics Committee of the medical institution, which will inform the coordinating and/or head investigator from each experimental site.
In this case, the investigator must notify his medical institution and the study initiator, providing in writing a detailed explanation of the reason that induced the study discontinuation.

14.3 Archiving

The investigator/experimental site is responsible for archiving the important documents of the study as specified in the GCP and in accordance with the applicable regulatory requirements. The investigator/experimental site should take the necessary measures to prevent the accidental or premature destruction of the documents.
The investigator/experimental site must preserve the important documents of the study for at least two years after the last approval of the claim for an Authorization of Introducing in Commerce (AIC) and until no other claim for AIC is presumable, or at least two years after the formal interruption of the investigated product development.
However, these documents could be stored for a longer period then required by the applicable regulations or by the agreement with the study initiator.
The study initiator should inform in writing the investigator/experimental site when the preservation of study documents will be no longer necessary.

14.4 Confidentiality and publication policy

The investigator recognize that all acquired informations are the property of **Iperboreal Pharma S.r.l.** and, therefore, all informations regarding the investigated product (indications, patents, chemical formula, synthesis processes, experimental data or other relevant informations) should not be disclosed.
The investigator may use these informations exclusively for performing the research. Iperboreal Pharma S.r.l. will use the data derived from clinical study in connection with development of the pharmacological product. Hence, it may transmit these results to other investigators and to the competent authorities.
As regards the data derived from this clinical study, the investigator is compelled to provide all the results to the study initiator. The study head investigator and study coordinator will have full access to all data derived from this clinical study. The investigators are not allowed to publish or present in any form (oral/poster presentation) the results of this study, either in part or in total, without a written permission from the part of **Iperboreal Pharma S.r.l.**
Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscript Submitted to Biomedical Journals (International Committee

of Medical Journal Editors, 1997). The study initiator is entitled to delay publication in order to obtain patent protection.

14.5 Insurance of Civic Responsibility

This study is covered by an insurance policy for civic responsibility in front of third parties as stated by **Iperboreal Pharma S.r.l.** together with Insurance Company, which is responsible for reimbursement of the costs that should be paid in quality of civic responsibility in the sense of law, as damages (interest, expenses) for any possible injury to the subject induced by medical products, registered or not, administered during the clinical trial according to the study protocol.

14.6 Financial sustenance of the study

The financial issues related to this study will be described in a separate "Financial Agreement" between **Iperboreal Pharma S.r.l.** and the institutions involved in the study.

15 INVESTIGATOR'S RESPONSABILITIES

The coordinating investigator shall be responsible in front of the study initiator for all the actions transferred to other members of his staff designated to perform the study.
If not otherwise specified, the term "Investigator" used in this study protocol and in the Case Report Form means the coordinating investigator or a qualified person assigned by him, which is able to assure the study-related activities and to sign the study documents in his name.
The investigator should conduct the study in accordance with study protocol and also with the Good Clinical Practice guidelines (ICH-E6) and principles of the Declaration of Helsinki (1964) with subsequent revisions (**Appendix II**).

16 FINAL STUDY REPORT

Within 6 months after conclusion of the study, head-investigator and/or study initiator and/or a delegate person shall write a Final Clinical Report containing clinical comments based on the data provided by the statistical analysis. If another person then study initiator itself will conceive Final Clinical Report, it should be revised and approved by the study initiator.

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APPENDIX I

SUBJECTIVE QUESTIONNAIRE ON THE PATIENT'S PERCEPTION OF WELL BEING

1 **Rispetto a un mese fa, come giudicherebbe il Suo attuale stato di salute ?**

Decisamente migliore adesso rispetto ad un mese fa	Leggermente migliore adesso rispetto ad un mese fa	Più o meno uguale ad un mese fa	Leggermente peggiore adesso rispetto ad un mese fa	Decisamente peggiore adesso rispetto ad un mese fa
▼	▼	▼	▼	▼
☐1	☐2	☐3	☐4	☐5

2 Nelle ultime quattro settimane in che misura ciascuno dei seguenti sintomi Le ha creato problemi?

	PER NIENTE	UN PO'	ABBASTANZA	MOLTO	MOLTISSIMO
	▼	▼	▼	▼	▼
a. NAUSEA	☐1	☐2	☐3	☐4	☐5
b. MANCANZA DI APPETITO	☐1	☐2	☐3	☐4	☐5
c. STIPSI	☐1	☐2	☐3	☐4	☐5
d. DIARREA	☐1	☐2	☐3	☐4	☐5
e. MAL DI STOMACO	☐1	☐2	☐3	☐4	☐5
f. DOLORI MUSCOLARI	☐1	☐2	☐3	☐4	☐5
g. CRAMPI MUSCOLARI	☐1	☐2	☐3	☐4	☐5
h. PRURITO	☐1	☐2	☐3	☐4	☐5
i. RESPIRO CORTO, DIFFICOLTÀ RESPIRATORIE	☐1	☐2	☐3	☐4	☐5
j. DOLORE TORACICO	☐1	☐2	☐3	☐4	☐5
k. AFFATICAMENTO (sentirsi svuotati, a pezzi)	☐1	☐2	☐3	☐4	☐5
l. SENSAZIONE DI SVENIMENTO CAPOGIRI	☐1	☐2	☐3	☐4	☐5
m. INTORPIDIMENTO, FORMICOLIO ALLE MANI ED AI PIEDI	☐1	☐2	☐3	☐4	☐5
n. PROBLEMI CON IL CATETERE PERITONEALE	☐1	☐2	☐3	☐4	☐5

APPENDIX II

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any

possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the

study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

19th March 2018

Iperboreal Pharma srl - Via Piave, 110/7 - 65122 Pescara (PE) - Italy
P.IVA 01702360684

16.1.2 SAMPLE CASE REPORT FORM

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code **Randomization Code**

Informed Consent

ICF signed, dated and copy provided to the subject ○ yes ○ no

Annotated eCRF		
Variable	**Type**	**Details**
consent_signed	radio	yes => 1 no => 2

Date of signature *dd/mm/yyyy*

Annotated eCRF		
Variable	**Type**	**Details**
consent_date	date	-

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - Visit Date

Visit Date *dd/mm/yyyy*

Annotated eCRF

Variable	**Type**	**Details**
visdat	date	-

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code **Randomization Code**

Screening Period: Day -28 - Demographic Data

Type of Patient ○ Hospitalized patient ○ Outpatient patient

Annotated eCRF		
Variable	**Type**	**Details**
patgrp	radio	Hospitalized patient => 1 Outpatient patient => 2

Sex ○ Male ○ Female

Annotated eCRF		
Variable	**Type**	**Details**
sex	radio	Male => M Female => F

Date of birth *dd/mm/yyyy*

Annotated eCRF		
Variable	**Type**	**Details**
brthdat	date	-

Calculated Age (years)

Annotated eCRF		
Variable	**Type**	**Details**
age	int	Length (2)

Race ○ White ○ Black ○ Asian ○ Hispanic ○ Other

Annotated eCRF		
Variable	**Type**	**Details**
race	radio	White => W Black => B Asian => A Hispanic => H Other => O

If other, please specify

Annotated eCRF		
Variable	**Type**	**Details**
raceoth	text	Length (50)

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - Medical and Surgical History

Does the patient have any significant medical or surgical history? ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
mhyn	radio	Yes => Y No => N

If Yes, complete this section

Disease/Surgery (prior and/or concomitant)

Date of Diagnosis *na/na/na*

Date of Resolution *na/na/na*

Ongoing ☐

Annotated eCRF		
Variable	**Type**	**Details**
mhterm	text	Length (100)
mhstdat	partial_date_ymd	-
mhendat	partial_date_ymd	-
mhongo	checkbox	1/0 (True/False)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - Concomitant Medications in the last 3 months

Has the patient taken any treatment in the last 3 months? ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
cmyn	radio	Yes => Y No => N

If Yes, complete the Previous and Concomitant Medication form

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - Physical examitnation

Was the physical examination performed? ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
peferf	radio	Yes => Y No => N

Are there any abnormalities? ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
peclsig	radio	Yes => Y No => N

In case of clinically abnormalities please fill in the table.

Code **(34)**

Description

Annotated eCRF		
Variable	**Type**	**Details**
petest	select	=> Eyes => 01 Ears, Nose, Throat => 02 Head and Neck => 03 Cardiovascular => 04 Lungs => 05 Abdomen => 06 Musculoskeletal => 07 Lymph nodes => 08 Skin => 09 Urogenital System => 10 Nervous System => 11 Mental State => 12 Other => 99
peorres	text	Length (100)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - Clinical Parameters

Result	**Not Done**
Height (cm)	

Annotated eCRF

Variable	**Type**	**Details**
height	int	Length (3)
heightnd	checkbox	1/0 (True/False)

	Not Done
Weight (kg)	

Annotated eCRF

Variable	**Type**	**Details**
weight	decimal	Length (4,1)
weightnd	checkbox	1/0 (True/False)

Systolic Blood Pressure (mmHg) **(33)**

Annotated eCRF

Variable	**Type**	**Details**
sysbp	int	Length (3)
sysbpnd	checkbox	1/0 (True/False)
sysbpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diastolic Blood Pressure (mmHg) **(33)**

Annotated eCRF

Variable	**Type**	**Details**
diabp	int	Length (3)
diabpnd	checkbox	1/0 (True/False)
diabpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Heart Rate (beats/min) **(33)**

Annotated eCRF

Variable	**Type**	**Details**
hr	int	Length (3)
hrnd	checkbox	1/0 (True/False)
hrev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diuresis (L/day)

Annotated eCRF

Variable	**Type**	**Details**
diuresis	decimal	Length (4,2)

Does the patient show hyperhydratation signs? Yes No

Annotated eCRF

Variable	**Type**	**Details**
hydrayn	radio	Yes => Y No => N

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - Pregnancy Test

Was the pregancy test done? ○ Yes ○ No ○ Na

Annotated eCRF		
Variable	**Type**	**Details**
pregyn	radio	Yes => Y No => N Na => Na

Date *dd/mm/yyyy*

Annotated eCRF		
Variable	**Type**	**Details**
pregdat	date	-

Result ○ Positive ○ Negative

Annotated eCRF		
Variable	**Type**	**Details**
pregres	radio	Positive => Pos Negative => Neg

If the test is POSITIVE the patient cannot be enrolled in the study

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - Ultrafiltration

1st Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval1	int	Length (5)

2nd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval2	int	Length (5)

3rd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval3	int	Length (5)

Nocturnal Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval4	int	Length (5)

Total ultrafiltration (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagtot	int	Length (5)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - CA 125

CA 125 (U.a./mL)

Annotated eCRF

Variable	**Type**	**Details**
ca125val	decimal	Length (8,1)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - Proteins in Ultrafiltration

Proteins in ultrafiltration (g/dL)

Annotated eCRF		
Variable	**Type**	**Details**
protval	decimal	Length (8,1)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - Uric Acid

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	**Type**	**Details**
lbdat1	date	-

Value	**Unit**	**Low Range**	**High Range**	**Not Done**	**Evaluation**
Uric Acid					**(33)**

Annotated eCRF

Variable	**Type**	**Details**
urate_r	decimal	Length (8,2)
urate_u	text	Length (15)
urate_lo	decimal	Length (8,2)
urate_hi	decimal	Length (8,2)
urate_nd	checkbox	1/0 (True/False)
urate_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Screening Period: Day -28 - Hematology

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast	radio	Yes => Y No => N

Value	Unit	Low Range	High Range	Not Done	Evaluation
RBC count				☐	(33)

Annotated eCRF

Variable	Type	Details
rbc_r	decimal	Length (8,2)
rbc_u	text	Length (15)
rbc_lo	decimal	Length (8,2)
rbc_hi	decimal	Length (8,2)
rbc_nd	checkbox	1/0 (True/False)
rbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
Hematocrit				☐	(33)

Annotated eCRF

Variable	Type	Details
hct_r	decimal	Length (8,2)
hct_u	text	Length (15)
hct_lo	decimal	Length (8,2)
hct_hi	decimal	Length (8,2)
hct_nd	checkbox	1/0 (True/False)
hct_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
Hemoglobin				☐	(33)

Annotated eCRF

Variable	Type	Details
hgb_r	decimal	Length (8,2)
hgb_u	text	Length (15)
hgb_lo	decimal	Length (8,2)
hgb_hi	decimal	Length (8,2)
hgb_nd	checkbox	1/0 (True/False)
hgb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
WBC				☐	(33)

Annotated eCRF

Variable	Type	Details
wbc_r	decimal	Length (8,2)
wbc_u	text	Length (15)

wbc_lo	decimal	Length (8,2)
wbc_hi	decimal	Length (8,2)
wbc_nd	checkbox	1/0 (True/False)
wbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Neutrophils (33)

Annotated eCRF

Variable	Type	Details
neut_r	decimal	Length (8,2)
neut_u	text	Length (15)
neut_lo	decimal	Length (8,2)
neut_hi	decimal	Length (8,2)
neut_nd	checkbox	1/0 (True/False)
neut_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Basophils (33)

Annotated eCRF

Variable	Type	Details
baso_r	decimal	Length (8,2)
baso_u	text	Length (15)
baso_lo	decimal	Length (8,2)
baso_hi	decimal	Length (8,2)
baso_nd	checkbox	1/0 (True/False)
baso_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Eosinophils (33)

Annotated eCRF

Variable	Type	Details
eos_r	decimal	Length (8,2)
eos_u	text	Length (15)
eos_lo	decimal	Length (8,2)
eos_hi	decimal	Length (8,2)
eos_nd	checkbox	1/0 (True/False)
eos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Lymphocytes (33)

Annotated eCRF

Variable	Type	Details
lym_r	decimal	Length (8,2)
lym_u	text	Length (15)
lym_lo	decimal	Length (8,2)
lym_hi	decimal	Length (8,2)
lym_nd	checkbox	1/0 (True/False)
lym_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Monocytes (33)

Annotated eCRF

Variable	Type	Details
mono_r	decimal	Length (8,2)
mono_u	text	Length (15)
mono_lo	decimal	Length (8,2)
mono_hi	decimal	Length (8,2)
mono_nd	checkbox	1/0 (True/False)
mono_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Platelet count (33)

Annotated eCRF

Variable	Type	Details
plat_r	decimal	Length (8,2)
plat_u	text	Length (15)
plat_lo	decimal	Length (8,2)
plat_hi	decimal	Length (8,2)
plat_nd	checkbox	1/0 (True/False)
plat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Screening Period: Day -28 - Clinical Chemistry

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat3	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast1	radio	Yes => Y No => N

	Value	Unit	Low Range	High Range	Not Done	Evaluation
BUN / Azotemia					☐	(33)

Annotated eCRF

Variable	Type	Details
bun_r	decimal	Length (8,2)
bun_u	text	Length (15)
bun_lo	decimal	Length (8,2)
bun_hi	decimal	Length (8,2)
bun_nd	checkbox	1/0 (True/False)
bun_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Creatinine					☐	(33)

Annotated eCRF

Variable	Type	Details
creat_r	decimal	Length (8,2)
creat_u	text	Length (15)
creat_lo	decimal	Length (8,2)
creat_hi	decimal	Length (8,2)
creat_nd	checkbox	1/0 (True/False)
creat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Glucose					☐	(33)

Annotated eCRF

Variable	Type	Details
gluc_r	decimal	Length (8,2)
gluc_u	text	Length (15)
gluc_lo	decimal	Length (8,2)
gluc_hi	decimal	Length (8,2)
gluc_nd	checkbox	1/0 (True/False)
gluc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Cholesterol					☐	(33)

Annotated eCRF

Variable	Type	Details
chol_r	decimal	Length (8,2)
chol_u	text	Length (15)

chol_lo	decimal	Length (8,2)
chol_hi	decimal	Length (8,2)
chol_nd	checkbox	1/0 (True/False)
chol_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

HDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
hdl_r	decimal	Length (8,2)
hdl_u	text	Length (15)
hdl_lo	decimal	Length (8,2)
hdl_hi	decimal	Length (8,2)
hdl_nd	checkbox	1/0 (True/False)
hdl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

LDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
ldl_r	decimal	Length (8,2)
ldl_u	text	Length (15)
ldl_lo	decimal	Length (8,2)
ldl_hi	decimal	Length (8,2)
ldl_nd	checkbox	1/0 (True/False)
ldl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Triglycerides (33)

Annotated eCRF

Variable	Type	Details
trig_r	decimal	Length (8,2)
trig_u	text	Length (15)
trig_lo	decimal	Length (8,2)
trig_hi	decimal	Length (8,2)
trig_nd	checkbox	1/0 (True/False)
trig_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Proteins (33)

Annotated eCRF

Variable	Type	Details
prot_r	decimal	Length (8,2)
prot_u	text	Length (15)
prot_lo	decimal	Length (8,2)
prot_hi	decimal	Length (8,2)
prot_nd	checkbox	1/0 (True/False)
prot_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Albumin (33)

Annotated eCRF

Variable	Type	Details
alb_r	decimal	Length (8,2)
alb_u	text	Length (15)
alb_lo	decimal	Length (8,2)
alb_hi	decimal	Length (8,2)
alb_nd	checkbox	1/0 (True/False)
alb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Bilirubin (33)

Annotated eCRF

Variable	Type	Details
bili_r	decimal	Length (8,2)
bili_u	text	Length (15)
bili_lo	decimal	Length (8,2)
bili_hi	decimal	Length (8,2)
bili_nd	checkbox	1/0 (True/False)
bili_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGOT (AST) (33)

Annotated eCRF

Variable	Type	Details
ast_r	decimal	Length (8,2)
ast_u	text	Length (15)
ast_lo	decimal	Length (8,2)
ast_hi	decimal	Length (8,2)
ast_nd	checkbox	1/0 (True/False)
ast_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGPT (ALT) (33)

Annotated eCRF

Variable	Type	Details
alt_r	decimal	Length (8,2)
alt_u	text	Length (15)
alt_lo	decimal	Length (8,2)
alt_hi	decimal	Length (8,2)
alt_nd	checkbox	1/0 (True/False)
alt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Alkaline Phosphatase (33)

Annotated eCRF

Variable	Type	Details
alp_r	decimal	Length (8,2)
alp_u	text	Length (15)
alp_lo	decimal	Length (8,2)
alp_hi	decimal	Length (8,2)
alp_nd	checkbox	1/0 (True/False)
alp_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

GGT (33)

Annotated eCRF

Variable	Type	Details
ggt_r	decimal	Length (8,2)
ggt_u	text	Length (15)
ggt_lo	decimal	Length (8,2)
ggt_hi	decimal	Length (8,2)
ggt_nd	checkbox	1/0 (True/False)
ggt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Serum Sodium (33)

Annotated eCRF

Variable	Type	Details
sodium_r	decimal	Length (8,2)
sodium_u	text	Length (15)
sodium_lo	decimal	Length (8,2)
sodium_hi	decimal	Length (8,2)
sodium_nd	checkbox	1/0 (True/False)
sodium_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Potassium (33)

Annotated eCRF

Variable	Type	Details
k_r	decimal	Length (8,2)
k_u	text	Length (15)
k_lo	decimal	Length (8,2)
k_hi	decimal	Length (8,2)
k_nd	checkbox	1/0 (True/False)
k_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Calcium (33)

Annotated eCRF

Variable	Type	Details
ca_r	decimal	Length (8,2)
ca_u	text	Length (15)
ca_lo	decimal	Length (8,2)
ca_hi	decimal	Length (8,2)
ca_nd	checkbox	1/0 (True/False)
ca_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Phosphorus (33)

Annotated eCRF

Variable	Type	Details
phos_r	decimal	Length (8,2)
phos_u	text	Length (15)
phos_lo	decimal	Length (8,2)
phos_hi	decimal	Length (8,2)
phos_nd	checkbox	1/0 (True/False)

phos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - Inclusion Criteria

Age ≥18 years ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
inc01	radio	Yes => Y No => N

Diagnosis of ESRD treated for at least three month with CAPD, as stated by the medical staff of the center ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
inc02	radio	Yes => Y No => N

Stable clinical condition within four weeks before screening period, certified by medical/surgical history, physical examination and laboratory exploration ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
inc03	radio	Yes => Y No => N

Hemoglobin level ≥9g/dL ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
inc04	radio	Yes => Y No => N

Absence of acute peritonitis and/or peritoneal catheter infection (either exit site or subcutaneous tunnel) episodes within three months before selection ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
inc05	radio	Yes => Y No => N

To understand and sign an informed consent form ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
inc06	radio	Yes => Y No => N

For patients who will be included in Group B, the following criteria must be fulfilled too:

Be treated with Extraneal (nocturnal exchange bag solution) for at least 1 month ○ Yes ○ No ○ Na

		Annotated eCRF
Variable	**Type**	**Details**
inc07	radio	Yes => Y No => N Na => Na

Be treated with 1, 2 or 3 diurnal exchange bag solutions (solution bags with 1,5% glucose) and one nocturnal exchange bag solution with icodextrin (Extraneal) ○ Yes ○ No ○ Na

		Annotated eCRF
Variable	**Type**	**Details**
inc08	radio	Yes => Y No => N Na => Na

If one inclusion criterion is answered with "No" the patient is not eligible for this study.

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day -28 - Exclusion Criteria

History of alcohol or drug abuse in the last six months before selection for the study; ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
exc01	radio	Yes => Y No => N

Androgen therapy in the last six months before selection ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
exc02	radio	Yes => Y No => N

Active infections ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
exc03	radio	Yes => Y No => N

History of congestive heart failure stage III and IV NYHA ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
exc04	radio	Yes => Y No => N

History of major cardiovascular events like stroke, acute myocardial infarction, coronary or other arterial revascularization procedures in the last three months before selection ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
exc05	radio	Yes => Y No => N

Clinically relevant cardiac arrhythmia ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
exc06	radio	Yes => Y No => N

Clinically relevant abnormalities of functional hepatic tests; ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
exc07	radio	Yes => Y No => N

Therapy with L-carnitine or its derivatives in the last three months before selection ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
exc08	radio	Yes => Y No => N

Pregnancy, lactating women or female subjects of childbearing potential who do not use an effective method of contraception ○ Yes ○ No ○ Na

Annotated eCRF		
Variable	**Type**	**Details**
exc09	radio	Yes => Y No => N Na => Na

Presence of relevant chronic medical conditions that could suggest exclusion of patient from the study or could interfere with assessment of study parameters, especially if the life expectation is less than one year ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
exc10	radio	Yes => Y No => N

Participation in another clinical study within the past month ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
exc11	radio	Yes => Y No => N

Known allergic reactions to L-carnitine or xylitol ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
exc12	radio	Yes => Y No => N

If one exclusion criterion is answered with "Yes" the patient is not eligible for this study.

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - Visit Date

Visit Date *dd/mm/yyyy*

Annotated eCRF

Variable	**Type**	**Details**
visdat	date	-

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - Clinical Parameters

		Not Done	
Weight (kg)		☐	

Annotated eCRF

Variable	**Type**	**Details**
weight	decimal	Length (4,1)
weightnd	checkbox	1/0 (True/False)

Systolic Blood Pressure (mmHg)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
sysbp	int	Length (3)
sysbpnd	checkbox	1/0 (True/False)
sysbpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diastolic Blood Pressure (mmHg)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
diabp	int	Length (3)
diabpnd	checkbox	1/0 (True/False)
diabpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Heart Rate (beats/min)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
hr	int	Length (3)
hrnd	checkbox	1/0 (True/False)
hrev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diuresis (L/day)

Annotated eCRF

Variable	**Type**	**Details**
diuresis	decimal	Length (4,2)

Does the patient show hyperhydratation signs? ○ Yes ○ No

Annotated eCRF

Variable	**Type**	**Details**
hydrayn	radio	Yes => Y No => N

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - Concomitant Medications

Has there been a change in the concomitant medications? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
cmyn1	radio	Yes => Y No => N

If Yes, complete the Previous and Concomitant Medication form

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - Adverse Events

Were there changes in the concomitant diseases or the patient experienced any adverse event? ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
aeyn	radio	Yes => Y No => N

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - Subjective Questionnaire

Did the patient fill in the subjective questionnaire ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
qsyn	radio	Yes => Y No => N

Total Score

		Annotated eCRF
Variable	**Type**	**Details**
qstot	int	Length (3)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - Weekly Total Urea Kt/V

Total Urea Kt/V (/week)

Annotated eCRF

Variable	**Type**	**Details**
ureaval	decimal	Length (8,2)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code **Randomization Code**

Screening Period: Day 0 - Peritoneal Equilibration Test (PET)

Dialysate/Plasma Creatinine

Annotated eCRF

Variable	Type	Details
petval	decimal	Length (8,2)

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - Weekly Total Creatine Clearance

Creatine Clearance (/week)

Annotated eCRF

Variable	**Type**	**Details**
creatval	decimal	Length (8,2)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - Ultrafiltration

1st Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval1	int	Length (5)

2nd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval2	int	Length (5)

3rd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval3	int	Length (5)

Nocturnal Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval4	int	Length (5)

Total ultrafiltration (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagtot	int	Length (5)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - CA 125

CA 125 (U.a./mL)

Annotated eCRF

Variable	**Type**	**Details**
ca125val	decimal	Length (8,1)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - Proteins in Ultrafiltration

Proteins in ultrafiltration (g/dL)

Annotated eCRF		
Variable	**Type**	**Details**
protval	decimal	Length (8,1)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - Uric and Lactic Acid

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat2	date	-

Value	Unit	Low Range	High Range	Not Done	Evaluation
Uric Acid				☐	(33)

Annotated eCRF

Variable	Type	Details
urate_r	decimal	Length (8,2)
urate_u	text	Length (15)
urate_lo	decimal	Length (8,2)
urate_hi	decimal	Length (8,2)
urate_nd	checkbox	1/0 (True/False)
urate_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
Lactic Acid				☐	(33)

Annotated eCRF

Variable	Type	Details
lacti_r	decimal	Length (8,2)
lacti_u	text	Length (15)
lacti_lo	decimal	Length (8,2)
lacti_hi	decimal	Length (8,2)
lacti_nd	checkbox	1/0 (True/False)
lacti_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Screening Period: Day 0 - Hematology

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast	radio	Yes => Y No => N

Value	Unit	Low Range	High Range	Not Done	Evaluation
RBC count				☐	(33)

Annotated eCRF

Variable	Type	Details
rbc_r	decimal	Length (8,2)
rbc_u	text	Length (15)
rbc_lo	decimal	Length (8,2)
rbc_hi	decimal	Length (8,2)
rbc_nd	checkbox	1/0 (True/False)
rbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
Hematocrit				☐	(33)

Annotated eCRF

Variable	Type	Details
hct_r	decimal	Length (8,2)
hct_u	text	Length (15)
hct_lo	decimal	Length (8,2)
hct_hi	decimal	Length (8,2)
hct_nd	checkbox	1/0 (True/False)
hct_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
Hemoglobin				☐	(33)

Annotated eCRF

Variable	Type	Details
hgb_r	decimal	Length (8,2)
hgb_u	text	Length (15)
hgb_lo	decimal	Length (8,2)
hgb_hi	decimal	Length (8,2)
hgb_nd	checkbox	1/0 (True/False)
hgb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
WBC				☐	(33)

Annotated eCRF

Variable	Type	Details
wbc_r	decimal	Length (8,2)
wbc_u	text	Length (15)

wbc_lo	decimal	Length (8,2)
wbc_hi	decimal	Length (8,2)
wbc_nd	checkbox	1/0 (True/False)
wbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Neutrophils (33)

Annotated eCRF

Variable	Type	Details
neut_r	decimal	Length (8,2)
neut_u	text	Length (15)
neut_lo	decimal	Length (8,2)
neut_hi	decimal	Length (8,2)
neut_nd	checkbox	1/0 (True/False)
neut_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Basophils (33)

Annotated eCRF

Variable	Type	Details
baso_r	decimal	Length (8,2)
baso_u	text	Length (15)
baso_lo	decimal	Length (8,2)
baso_hi	decimal	Length (8,2)
baso_nd	checkbox	1/0 (True/False)
baso_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Eosinophils (33)

Annotated eCRF

Variable	Type	Details
eos_r	decimal	Length (8,2)
eos_u	text	Length (15)
eos_lo	decimal	Length (8,2)
eos_hi	decimal	Length (8,2)
eos_nd	checkbox	1/0 (True/False)
eos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Lymphocytes (33)

Annotated eCRF

Variable	Type	Details
lym_r	decimal	Length (8,2)
lym_u	text	Length (15)
lym_lo	decimal	Length (8,2)
lym_hi	decimal	Length (8,2)
lym_nd	checkbox	1/0 (True/False)
lym_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Monocytes (33)

Annotated eCRF

Variable	Type	Details
mono_r	decimal	Length (8,2)
mono_u	text	Length (15)
mono_lo	decimal	Length (8,2)
mono_hi	decimal	Length (8,2)
mono_nd	checkbox	1/0 (True/False)
mono_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Platelet count (33)

Annotated eCRF

Variable	Type	Details
plat_r	decimal	Length (8,2)
plat_u	text	Length (15)
plat_lo	decimal	Length (8,2)
plat_hi	decimal	Length (8,2)
plat_nd	checkbox	1/0 (True/False)
plat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Screening Period: Day 0 - Clinical Chemistry

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat3	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast1	radio	Yes => Y No => N

	Value	Unit	Low Range	High Range	Not Done	Evaluation
BUN / Azotemia					☐	(33)

Annotated eCRF

Variable	Type	Details
bun_r	decimal	Length (8,2)
bun_u	text	Length (15)
bun_lo	decimal	Length (8,2)
bun_hi	decimal	Length (8,2)
bun_nd	checkbox	1/0 (True/False)
bun_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Creatinine					☐	(33)

Annotated eCRF

Variable	Type	Details
creat_r	decimal	Length (8,2)
creat_u	text	Length (15)
creat_lo	decimal	Length (8,2)
creat_hi	decimal	Length (8,2)
creat_nd	checkbox	1/0 (True/False)
creat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Glucose					☐	(33)

Annotated eCRF

Variable	Type	Details
gluc_r	decimal	Length (8,2)
gluc_u	text	Length (15)
gluc_lo	decimal	Length (8,2)
gluc_hi	decimal	Length (8,2)
gluc_nd	checkbox	1/0 (True/False)
gluc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Cholesterol					☐	(33)

Annotated eCRF

Variable	Type	Details
chol_r	decimal	Length (8,2)
chol_u	text	Length (15)

chol_lo	decimal	Length (8,2)
chol_hi	decimal	Length (8,2)
chol_nd	checkbox	1/0 (True/False)
chol_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

HDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
hdl_r	decimal	Length (8,2)
hdl_u	text	Length (15)
hdl_lo	decimal	Length (8,2)
hdl_hi	decimal	Length (8,2)
hdl_nd	checkbox	1/0 (True/False)
hdl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

LDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
ldl_r	decimal	Length (8,2)
ldl_u	text	Length (15)
ldl_lo	decimal	Length (8,2)
ldl_hi	decimal	Length (8,2)
ldl_nd	checkbox	1/0 (True/False)
ldl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Triglycerides (33)

Annotated eCRF

Variable	Type	Details
trig_r	decimal	Length (8,2)
trig_u	text	Length (15)
trig_lo	decimal	Length (8,2)
trig_hi	decimal	Length (8,2)
trig_nd	checkbox	1/0 (True/False)
trig_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Proteins (33)

Annotated eCRF

Variable	Type	Details
prot_r	decimal	Length (8,2)
prot_u	text	Length (15)
prot_lo	decimal	Length (8,2)
prot_hi	decimal	Length (8,2)
prot_nd	checkbox	1/0 (True/False)
prot_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Albumin (33)

Annotated eCRF

Variable	Type	Details
alb_r	decimal	Length (8,2)
alb_u	text	Length (15)
alb_lo	decimal	Length (8,2)
alb_hi	decimal	Length (8,2)
alb_nd	checkbox	1/0 (True/False)
alb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Bilirubin					**(33)**

Annotated eCRF

Variable	Type	Details
bili_r	decimal	Length (8,2)
bili_u	text	Length (15)
bili_lo	decimal	Length (8,2)
bili_hi	decimal	Length (8,2)
bili_nd	checkbox	1/0 (True/False)
bili_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGOT (AST)					**(33)**

Annotated eCRF

Variable	Type	Details
ast_r	decimal	Length (8,2)
ast_u	text	Length (15)
ast_lo	decimal	Length (8,2)
ast_hi	decimal	Length (8,2)
ast_nd	checkbox	1/0 (True/False)
ast_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGPT (ALT)					**(33)**

Annotated eCRF

Variable	Type	Details
alt_r	decimal	Length (8,2)
alt_u	text	Length (15)
alt_lo	decimal	Length (8,2)
alt_hi	decimal	Length (8,2)
alt_nd	checkbox	1/0 (True/False)
alt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Alkaline Phosphatase					**(33)**

Annotated eCRF

Variable	Type	Details
alp_r	decimal	Length (8,2)
alp_u	text	Length (15)
alp_lo	decimal	Length (8,2)
alp_hi	decimal	Length (8,2)
alp_nd	checkbox	1/0 (True/False)
alp_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

GGT (33)

Annotated eCRF

Variable	Type	Details
ggt_r	decimal	Length (8,2)
ggt_u	text	Length (15)
ggt_lo	decimal	Length (8,2)
ggt_hi	decimal	Length (8,2)
ggt_nd	checkbox	1/0 (True/False)
ggt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Serum Sodium (33)

Annotated eCRF

Variable	Type	Details
sodium_r	decimal	Length (8,2)
sodium_u	text	Length (15)
sodium_lo	decimal	Length (8,2)
sodium_hi	decimal	Length (8,2)
sodium_nd	checkbox	1/0 (True/False)
sodium_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Potassium (33)

Annotated eCRF

Variable	Type	Details
k_r	decimal	Length (8,2)
k_u	text	Length (15)
k_lo	decimal	Length (8,2)
k_hi	decimal	Length (8,2)
k_nd	checkbox	1/0 (True/False)
k_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Calcium (33)

Annotated eCRF

Variable	Type	Details
ca_r	decimal	Length (8,2)
ca_u	text	Length (15)
ca_lo	decimal	Length (8,2)
ca_hi	decimal	Length (8,2)
ca_nd	checkbox	1/0 (True/False)
ca_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Phosphorus (33)

Annotated eCRF

Variable	Type	Details
phos_r	decimal	Length (8,2)
phos_u	text	Length (15)
phos_lo	decimal	Length (8,2)
phos_hi	decimal	Length (8,2)
phos_nd	checkbox	1/0 (True/False)

phos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - ECG

Is the ECG Normal? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
egnorm	radio	Yes => Y No => N

*In case of **Abnormality** please fill in the table below as appropriate*

ECG **(32)**

Evaluation **(31)**

Other, specify

Annotated eCRF

Variable	Type	Details
egtest	select	=> Sinus Arrhythmia => 1 Sinus Bradycardia => 2 Sinus Tachycardia => 3 Supraventricular Extrasystoles => 4 Ventricular Extrasystoles => 5 Atrial Flutter => 6 Right Bundle Branch Block => 7 Left Bundle Branch Block => 8 Left Anterior Hemiblock => 9 Left Posterior Hemiblock => 10 Incomplete Bundle Branch Block => 11 Non-specific Intraventricular Conduction Delay => 12 AV Block First Degree => 13 AV Block Second Degree Type 1 => 14 AV Block Second Degree Type 2 => 15 Right Atrial Hypertrophy => 16 Left Atrial Hypertrophy => 17 Right Ventricular Hypertrophy => 18 Left Ventricular Hypertrophy => 19 ST Segment Elevation => 20 Prolonged QT Interval => 21 Nonspecific T Wave Abnormalities => 22 Other => 99
egeval	select	=> Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4
ecothsp	text	Length (100)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Screening Period: Day 0 - Eligibility

Is the patient eligible to participate in the study? ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
ieyn	radio	Yes => Y No => N

If Yes please report the treatment number

		Annotated eCRF
Variable	**Type**	**Details**
trtnum	int	Length (4)

Treatment group ○ GROUP A ○ GROUP B

		Annotated eCRF
Variable	**Type**	**Details**
trtgrp	radio	GROUP A => 1 GROUP B => 2

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 14 - Visit Date

Visit Date *dd/mm/yyyy*

Annotated eCRF

Variable	**Type**	**Details**
visdat	date	-

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 14 - Clinical Parameters

		Not Done
Weight (kg)		☐

Annotated eCRF

Variable	**Type**	**Details**
weight	decimal	Length (4,1)
weightnd	checkbox	1/0 (True/False)

Systolic Blood Pressure (mmHg)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
sysbp	int	Length (3)
sysbpnd	checkbox	1/0 (True/False)
sysbpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diastolic Blood Pressure (mmHg)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
diabp	int	Length (3)
diabpnd	checkbox	1/0 (True/False)
diabpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Heart Rate (beats/min)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
hr	int	Length (3)
hrnd	checkbox	1/0 (True/False)
hrev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diuresis (L/day)

Annotated eCRF

Variable	**Type**	**Details**
diuresis	decimal	Length (4,2)

Does the patient show hyperhydratation signs? ○ Yes ○ No

Annotated eCRF

Variable	**Type**	**Details**
hydrayn	radio	Yes => Y No => N

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 14 - Treatment

Did patient complete treatment assigned since last visit? ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
trtyn	radio	Yes => Y No => N

Any missing dose? ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
dosmisyn	radio	Yes => Y No => N

If Yes, please specify

Annotated eCRF		
Variable	**Type**	**Details**
dosmisp	text	Length (100)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 14 - Concomitant Medications

Has there been a change in the concomitant medications? ○ Yes ○ No

Annotated eCRF

Variable	**Type**	**Details**
cmyn1	radio	Yes => Y No => N

If Yes, complete the Previous and Concomitant Medication form

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 14 - Adverse Events

Were there changes in the concomitant diseases or the patient experienced any adverse event? ○ Yes ○ No

Annotated eCRF

Variable	**Type**	**Details**
aeyn	radio	Yes => Y No => N

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 14 - Ultrafiltration

1st Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval1	int	Length (5)

2nd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval2	int	Length (5)

3rd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval3	int	Length (5)

Nocturnal Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval4	int	Length (5)

Total ultrafiltration (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagtot	int	Length (5)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 14 - CA 125

CA 125 (U.a./mL)

Annotated eCRF

Variable	**Type**	**Details**
ca125val	decimal	Length (8,1)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 14 - Proteins in Ultrafiltration

Proteins in ultrafiltration (g/dL)

Annotated eCRF

Variable	**Type**	**Details**
protval	decimal	Length (8,1)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 14 - Uric and Lactic Acid

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat2	date	-

Value	Unit	Low Range	High Range	Not Done	Evaluation
Uric Acid				☐	(33)

Annotated eCRF

Variable	Type	Details
urate_r	decimal	Length (8,2)
urate_u	text	Length (15)
urate_lo	decimal	Length (8,2)
urate_hi	decimal	Length (8,2)
urate_nd	checkbox	1/0 (True/False)
urate_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
Lactic Acid				☐	(33)

Annotated eCRF

Variable	Type	Details
lacti_r	decimal	Length (8,2)
lacti_u	text	Length (15)
lacti_lo	decimal	Length (8,2)
lacti_hi	decimal	Length (8,2)
lacti_nd	checkbox	1/0 (True/False)
lacti_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Intervention Period: Day 14 - Hematology

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast	radio	Yes => Y No => N

	Value	Unit	Low Range	High Range	Not Done	Evaluation
RBC count					☐	(33)

Annotated eCRF

Variable	Type	Details
rbc_r	decimal	Length (8,2)
rbc_u	text	Length (15)
rbc_lo	decimal	Length (8,2)
rbc_hi	decimal	Length (8,2)
rbc_nd	checkbox	1/0 (True/False)
rbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Hematocrit					☐	(33)

Annotated eCRF

Variable	Type	Details
hct_r	decimal	Length (8,2)
hct_u	text	Length (15)
hct_lo	decimal	Length (8,2)
hct_hi	decimal	Length (8,2)
hct_nd	checkbox	1/0 (True/False)
hct_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Hemoglobin					☐	(33)

Annotated eCRF

Variable	Type	Details
hgb_r	decimal	Length (8,2)
hgb_u	text	Length (15)
hgb_lo	decimal	Length (8,2)
hgb_hi	decimal	Length (8,2)
hgb_nd	checkbox	1/0 (True/False)
hgb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

WBC					☐	(33)

Annotated eCRF

Variable	Type	Details
wbc_r	decimal	Length (8,2)
wbc_u	text	Length (15)

wbc_lo	decimal	Length (8,2)
wbc_hi	decimal	Length (8,2)
wbc_nd	checkbox	1/0 (True/False)
wbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Neutrophils (33)

Annotated eCRF

Variable	Type	Details
neut_r	decimal	Length (8,2)
neut_u	text	Length (15)
neut_lo	decimal	Length (8,2)
neut_hi	decimal	Length (8,2)
neut_nd	checkbox	1/0 (True/False)
neut_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Basophils (33)

Annotated eCRF

Variable	Type	Details
baso_r	decimal	Length (8,2)
baso_u	text	Length (15)
baso_lo	decimal	Length (8,2)
baso_hi	decimal	Length (8,2)
baso_nd	checkbox	1/0 (True/False)
baso_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Eosinophils (33)

Annotated eCRF

Variable	Type	Details
eos_r	decimal	Length (8,2)
eos_u	text	Length (15)
eos_lo	decimal	Length (8,2)
eos_hi	decimal	Length (8,2)
eos_nd	checkbox	1/0 (True/False)
eos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Lymphocytes (33)

Annotated eCRF

Variable	Type	Details
lym_r	decimal	Length (8,2)
lym_u	text	Length (15)
lym_lo	decimal	Length (8,2)
lym_hi	decimal	Length (8,2)
lym_nd	checkbox	1/0 (True/False)
lym_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Monocytes (33)

Annotated eCRF

Variable	Type	Details
mono_r	decimal	Length (8,2)
mono_u	text	Length (15)
mono_lo	decimal	Length (8,2)
mono_hi	decimal	Length (8,2)
mono_nd	checkbox	1/0 (True/False)
mono_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Platelet count (33)

Annotated eCRF

Variable	Type	Details
plat_r	decimal	Length (8,2)
plat_u	text	Length (15)
plat_lo	decimal	Length (8,2)
plat_hi	decimal	Length (8,2)
plat_nd	checkbox	1/0 (True/False)
plat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Intervention Period: Day 14 - Clinical Chemistry

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat3	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast1	radio	Yes => Y No => N

	Value	Unit	Low Range	High Range	Not Done	Evaluation
BUN / Azotemia					☐	(33)

Annotated eCRF

Variable	Type	Details
bun_r	decimal	Length (8,2)
bun_u	text	Length (15)
bun_lo	decimal	Length (8,2)
bun_hi	decimal	Length (8,2)
bun_nd	checkbox	1/0 (True/False)
bun_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Creatinine					☐	(33)

Annotated eCRF

Variable	Type	Details
creat_r	decimal	Length (8,2)
creat_u	text	Length (15)
creat_lo	decimal	Length (8,2)
creat_hi	decimal	Length (8,2)
creat_nd	checkbox	1/0 (True/False)
creat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Glucose					☐	(33)

Annotated eCRF

Variable	Type	Details
gluc_r	decimal	Length (8,2)
gluc_u	text	Length (15)
gluc_lo	decimal	Length (8,2)
gluc_hi	decimal	Length (8,2)
gluc_nd	checkbox	1/0 (True/False)
gluc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Cholesterol					☐	(33)

Annotated eCRF

Variable	Type	Details
chol_r	decimal	Length (8,2)
chol_u	text	Length (15)

chol_lo	decimal	Length (8,2)
chol_hi	decimal	Length (8,2)
chol_nd	checkbox	1/0 (True/False)
chol_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

HDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
hdl_r	decimal	Length (8,2)
hdl_u	text	Length (15)
hdl_lo	decimal	Length (8,2)
hdl_hi	decimal	Length (8,2)
hdl_nd	checkbox	1/0 (True/False)
hdl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

LDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
ldl_r	decimal	Length (8,2)
ldl_u	text	Length (15)
ldl_lo	decimal	Length (8,2)
ldl_hi	decimal	Length (8,2)
ldl_nd	checkbox	1/0 (True/False)
ldl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Triglycerides (33)

Annotated eCRF

Variable	Type	Details
trig_r	decimal	Length (8,2)
trig_u	text	Length (15)
trig_lo	decimal	Length (8,2)
trig_hi	decimal	Length (8,2)
trig_nd	checkbox	1/0 (True/False)
trig_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Proteins (33)

Annotated eCRF

Variable	Type	Details
prot_r	decimal	Length (8,2)
prot_u	text	Length (15)
prot_lo	decimal	Length (8,2)
prot_hi	decimal	Length (8,2)
prot_nd	checkbox	1/0 (True/False)
prot_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Albumin (33)

Annotated eCRF

Variable	Type	Details
alb_r	decimal	Length (8,2)
alb_u	text	Length (15)
alb_lo	decimal	Length (8,2)
alb_hi	decimal	Length (8,2)
alb_nd	checkbox	1/0 (True/False)
alb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Bilirubin (33)

Annotated eCRF

Variable	Type	Details
bili_r	decimal	Length (8,2)
bili_u	text	Length (15)
bili_lo	decimal	Length (8,2)
bili_hi	decimal	Length (8,2)
bili_nd	checkbox	1/0 (True/False)
bili_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGOT (AST) (33)

Annotated eCRF

Variable	Type	Details
ast_r	decimal	Length (8,2)
ast_u	text	Length (15)
ast_lo	decimal	Length (8,2)
ast_hi	decimal	Length (8,2)
ast_nd	checkbox	1/0 (True/False)
ast_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGPT (ALT) (33)

Annotated eCRF

Variable	Type	Details
alt_r	decimal	Length (8,2)
alt_u	text	Length (15)
alt_lo	decimal	Length (8,2)
alt_hi	decimal	Length (8,2)
alt_nd	checkbox	1/0 (True/False)
alt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Alkaline Phosphatase (33)

Annotated eCRF

Variable	Type	Details
alp_r	decimal	Length (8,2)
alp_u	text	Length (15)
alp_lo	decimal	Length (8,2)
alp_hi	decimal	Length (8,2)
alp_nd	checkbox	1/0 (True/False)
alp_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

GGT (33)

Annotated eCRF

Variable	Type	Details
ggt_r	decimal	Length (8,2)
ggt_u	text	Length (15)
ggt_lo	decimal	Length (8,2)
ggt_hi	decimal	Length (8,2)
ggt_nd	checkbox	1/0 (True/False)
ggt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Serum Sodium (33)

Annotated eCRF

Variable	Type	Details
sodium_r	decimal	Length (8,2)
sodium_u	text	Length (15)
sodium_lo	decimal	Length (8,2)
sodium_hi	decimal	Length (8,2)
sodium_nd	checkbox	1/0 (True/False)
sodium_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Potassium (33)

Annotated eCRF

Variable	Type	Details
k_r	decimal	Length (8,2)
k_u	text	Length (15)
k_lo	decimal	Length (8,2)
k_hi	decimal	Length (8,2)
k_nd	checkbox	1/0 (True/False)
k_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Calcium (33)

Annotated eCRF

Variable	Type	Details
ca_r	decimal	Length (8,2)
ca_u	text	Length (15)
ca_lo	decimal	Length (8,2)
ca_hi	decimal	Length (8,2)
ca_nd	checkbox	1/0 (True/False)
ca_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Phosphorus (33)

Annotated eCRF

Variable	Type	Details
phos_r	decimal	Length (8,2)
phos_u	text	Length (15)
phos_lo	decimal	Length (8,2)
phos_hi	decimal	Length (8,2)
phos_nd	checkbox	1/0 (True/False)

phos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - Visit Date

Visit Date *dd/mm/yyyy*

Annotated eCRF

Variable	**Type**	**Details**
visdat	date	-

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - Clinical Parameters

			Not Done
Weight (kg)			☐

Annotated eCRF

Variable	**Type**	**Details**
weight	decimal	Length (4,1)
weightnd	checkbox	1/0 (True/False)

Systolic Blood Pressure (mmHg)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
sysbp	int	Length (3)
sysbpnd	checkbox	1/0 (True/False)
sysbpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diastolic Blood Pressure (mmHg)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
diabp	int	Length (3)
diabpnd	checkbox	1/0 (True/False)
diabpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Heart Rate (beats/min)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
hr	int	Length (3)
hrnd	checkbox	1/0 (True/False)
hrev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diuresis (L/day)

Annotated eCRF

Variable	**Type**	**Details**
diuresis	decimal	Length (4,2)

Does the patient show hyperhydratation signs? ○ Yes ○ No

Annotated eCRF

Variable	**Type**	**Details**
hydrayn	radio	Yes => Y No => N

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - Treatment

Did patient complete treatment assigned since last visit? ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
trtyn	radio	Yes => Y No => N

Any missing dose? ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
dosmisyn	radio	Yes => Y No => N

If Yes, please specify

Annotated eCRF		
Variable	**Type**	**Details**
dosmisp	text	Length (100)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - Concomitant Medications

Has there been a change in the concomitant medications? ○ Yes ○ No

Annotated eCRF

Variable	**Type**	**Details**
cmyn1	radio	Yes => Y No => N

If Yes, complete the Previous and Concomitant Medication form

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - Adverse Events

Were there changes in the concomitant diseases or the patient experienced any adverse event? ○ Yes ○ No

Annotated eCRF

Variable	**Type**	**Details**
aeyn	radio	Yes => Y No => N

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - Subjective Questionnaire

Did the patient fill in the subjective questionnaire ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
qsyn	radio	Yes => Y No => N

Total Score

Annotated eCRF		
Variable	**Type**	**Details**
qstot	int	Length (3)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - Weekly Total Urea Kt/V

Total Urea Kt/V (/week)

Annotated eCRF

Variable	**Type**	**Details**
ureaval	decimal	Length (8,2)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - Peritoneal Equilibration Test (PET)

Dialysate/Plasma Creatinine

Annotated eCRF

Variable	**Type**	**Details**
petval	decimal	Length (8,2)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code **Randomization Code**

Intervention Period: Day 28 - Weekly Total Creatine Clearance

Creatine Clearance (/week)

Annotated eCRF

Variable	Type	Details
creatval	decimal	Length (8,2)

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - Ultrafiltration

1st Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval1	int	Length (5)

2nd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval2	int	Length (5)

3rd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval3	int	Length (5)

Nocturnal Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval4	int	Length (5)

Total ultrafiltration (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagtot	int	Length (5)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - CA 125

CA 125 (U.a./mL)

Annotated eCRF

Variable	**Type**	**Details**
ca125val	decimal	Length (8,1)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - Proteins in Ultrafiltration

Proteins in ultrafiltration (g/dL)

Annotated eCRF

Variable	**Type**	**Details**
protval	decimal	Length (8,1)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - Uric and Lactic Acid

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat2	date	-

Value	Unit	Low Range	High Range	Not Done	Evaluation
Uric Acid				☐	(33)

Annotated eCRF

Variable	Type	Details
urate_r	decimal	Length (8,2)
urate_u	text	Length (15)
urate_lo	decimal	Length (8,2)
urate_hi	decimal	Length (8,2)
urate_nd	checkbox	1/0 (True/False)
urate_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
Lactic Acid				☐	(33)

Annotated eCRF

Variable	Type	Details
lacti_r	decimal	Length (8,2)
lacti_u	text	Length (15)
lacti_lo	decimal	Length (8,2)
lacti_hi	decimal	Length (8,2)
lacti_nd	checkbox	1/0 (True/False)
lacti_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Intervention Period: Day 28 - Hematology

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast	radio	Yes => Y No => N

Value	Unit	Low Range	High Range	Not Done	Evaluation
RBC count				☐	(33)

Annotated eCRF

Variable	Type	Details
rbc_r	decimal	Length (8,2)
rbc_u	text	Length (15)
rbc_lo	decimal	Length (8,2)
rbc_hi	decimal	Length (8,2)
rbc_nd	checkbox	1/0 (True/False)
rbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
Hematocrit				☐	(33)

Annotated eCRF

Variable	Type	Details
hct_r	decimal	Length (8,2)
hct_u	text	Length (15)
hct_lo	decimal	Length (8,2)
hct_hi	decimal	Length (8,2)
hct_nd	checkbox	1/0 (True/False)
hct_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
Hemoglobin				☐	(33)

Annotated eCRF

Variable	Type	Details
hgb_r	decimal	Length (8,2)
hgb_u	text	Length (15)
hgb_lo	decimal	Length (8,2)
hgb_hi	decimal	Length (8,2)
hgb_nd	checkbox	1/0 (True/False)
hgb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
WBC				☐	(33)

Annotated eCRF

Variable	Type	Details
wbc_r	decimal	Length (8,2)
wbc_u	text	Length (15)

wbc_lo	decimal	Length (8,2)
wbc_hi	decimal	Length (8,2)
wbc_nd	checkbox	1/0 (True/False)
wbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Neutrophils (33)

Annotated eCRF

Variable	Type	Details
neut_r	decimal	Length (8,2)
neut_u	text	Length (15)
neut_lo	decimal	Length (8,2)
neut_hi	decimal	Length (8,2)
neut_nd	checkbox	1/0 (True/False)
neut_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Basophils (33)

Annotated eCRF

Variable	Type	Details
baso_r	decimal	Length (8,2)
baso_u	text	Length (15)
baso_lo	decimal	Length (8,2)
baso_hi	decimal	Length (8,2)
baso_nd	checkbox	1/0 (True/False)
baso_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Eosinophils (33)

Annotated eCRF

Variable	Type	Details
eos_r	decimal	Length (8,2)
eos_u	text	Length (15)
eos_lo	decimal	Length (8,2)
eos_hi	decimal	Length (8,2)
eos_nd	checkbox	1/0 (True/False)
eos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Lymphocytes (33)

Annotated eCRF

Variable	Type	Details
lym_r	decimal	Length (8,2)
lym_u	text	Length (15)
lym_lo	decimal	Length (8,2)
lym_hi	decimal	Length (8,2)
lym_nd	checkbox	1/0 (True/False)
lym_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Monocytes (33)

Annotated eCRF

Variable	Type	Details
mono_r	decimal	Length (8,2)
mono_u	text	Length (15)
mono_lo	decimal	Length (8,2)
mono_hi	decimal	Length (8,2)
mono_nd	checkbox	1/0 (True/False)
mono_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Platelet count						**(33)**

Annotated eCRF

Variable	Type	Details
plat_r	decimal	Length (8,2)
plat_u	text	Length (15)
plat_lo	decimal	Length (8,2)
plat_hi	decimal	Length (8,2)
plat_nd	checkbox	1/0 (True/False)
plat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Intervention Period: Day 28 - Clinical Chemistry

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat3	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast1	radio	Yes => Y No => N

	Value	Unit	Low Range	High Range	Not Done	Evaluation
BUN / Azotemia					☐	(33)

Annotated eCRF

Variable	Type	Details
bun_r	decimal	Length (8,2)
bun_u	text	Length (15)
bun_lo	decimal	Length (8,2)
bun_hi	decimal	Length (8,2)
bun_nd	checkbox	1/0 (True/False)
bun_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Creatinine					☐	(33)

Annotated eCRF

Variable	Type	Details
creat_r	decimal	Length (8,2)
creat_u	text	Length (15)
creat_lo	decimal	Length (8,2)
creat_hi	decimal	Length (8,2)
creat_nd	checkbox	1/0 (True/False)
creat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Glucose					☐	(33)

Annotated eCRF

Variable	Type	Details
gluc_r	decimal	Length (8,2)
gluc_u	text	Length (15)
gluc_lo	decimal	Length (8,2)
gluc_hi	decimal	Length (8,2)
gluc_nd	checkbox	1/0 (True/False)
gluc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Cholesterol					☐	(33)

Annotated eCRF

Variable	Type	Details
chol_r	decimal	Length (8,2)
chol_u	text	Length (15)

chol_lo	decimal	Length (8,2)
chol_hi	decimal	Length (8,2)
chol_nd	checkbox	1/0 (True/False)
chol_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

HDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
hdl_r	decimal	Length (8,2)
hdl_u	text	Length (15)
hdl_lo	decimal	Length (8,2)
hdl_hi	decimal	Length (8,2)
hdl_nd	checkbox	1/0 (True/False)
hdl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

LDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
ldl_r	decimal	Length (8,2)
ldl_u	text	Length (15)
ldl_lo	decimal	Length (8,2)
ldl_hi	decimal	Length (8,2)
ldl_nd	checkbox	1/0 (True/False)
ldl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Triglycerides (33)

Annotated eCRF

Variable	Type	Details
trig_r	decimal	Length (8,2)
trig_u	text	Length (15)
trig_lo	decimal	Length (8,2)
trig_hi	decimal	Length (8,2)
trig_nd	checkbox	1/0 (True/False)
trig_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Proteins (33)

Annotated eCRF

Variable	Type	Details
prot_r	decimal	Length (8,2)
prot_u	text	Length (15)
prot_lo	decimal	Length (8,2)
prot_hi	decimal	Length (8,2)
prot_nd	checkbox	1/0 (True/False)
prot_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Albumin (33)

Annotated eCRF

Variable	Type	Details
alb_r	decimal	Length (8,2)
alb_u	text	Length (15)
alb_lo	decimal	Length (8,2)
alb_hi	decimal	Length (8,2)
alb_nd	checkbox	1/0 (True/False)
alb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Bilirubin (33)

Annotated eCRF

Variable	Type	Details
bili_r	decimal	Length (8,2)
bili_u	text	Length (15)
bili_lo	decimal	Length (8,2)
bili_hi	decimal	Length (8,2)
bili_nd	checkbox	1/0 (True/False)
bili_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGOT (AST) (33)

Annotated eCRF

Variable	Type	Details
ast_r	decimal	Length (8,2)
ast_u	text	Length (15)
ast_lo	decimal	Length (8,2)
ast_hi	decimal	Length (8,2)
ast_nd	checkbox	1/0 (True/False)
ast_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGPT (ALT) (33)

Annotated eCRF

Variable	Type	Details
alt_r	decimal	Length (8,2)
alt_u	text	Length (15)
alt_lo	decimal	Length (8,2)
alt_hi	decimal	Length (8,2)
alt_nd	checkbox	1/0 (True/False)
alt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Alkaline Phosphatase (33)

Annotated eCRF

Variable	Type	Details
alp_r	decimal	Length (8,2)
alp_u	text	Length (15)
alp_lo	decimal	Length (8,2)
alp_hi	decimal	Length (8,2)
alp_nd	checkbox	1/0 (True/False)
alp_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

GGT (33)

Annotated eCRF

Variable	Type	Details
ggt_r	decimal	Length (8,2)
ggt_u	text	Length (15)
ggt_lo	decimal	Length (8,2)
ggt_hi	decimal	Length (8,2)
ggt_nd	checkbox	1/0 (True/False)
ggt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Serum Sodium (33)

Annotated eCRF

Variable	Type	Details
sodium_r	decimal	Length (8,2)
sodium_u	text	Length (15)
sodium_lo	decimal	Length (8,2)
sodium_hi	decimal	Length (8,2)
sodium_nd	checkbox	1/0 (True/False)
sodium_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Potassium (33)

Annotated eCRF

Variable	Type	Details
k_r	decimal	Length (8,2)
k_u	text	Length (15)
k_lo	decimal	Length (8,2)
k_hi	decimal	Length (8,2)
k_nd	checkbox	1/0 (True/False)
k_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Calcium (33)

Annotated eCRF

Variable	Type	Details
ca_r	decimal	Length (8,2)
ca_u	text	Length (15)
ca_lo	decimal	Length (8,2)
ca_hi	decimal	Length (8,2)
ca_nd	checkbox	1/0 (True/False)
ca_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Phosphorus (33)

Annotated eCRF

Variable	Type	Details
phos_r	decimal	Length (8,2)
phos_u	text	Length (15)
phos_lo	decimal	Length (8,2)
phos_hi	decimal	Length (8,2)
phos_nd	checkbox	1/0 (True/False)

phos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Intervention Period: Day 28 - ECG

Is the ECG Normal? ○ Yes ○ No

Annotated eCRF		
Variable	**Type**	**Details**
egnorm	radio	Yes => Y No => N

*In case of **Abnormality** please fill in the table below as appropriate*

ECG **(32)**

Evaluation **(31)**

Other, specify

Annotated eCRF		
Variable	**Type**	**Details**
egtest	select	=> Sinus Arrhythmia => 1 Sinus Bradycardia => 2 Sinus Tachycardia => 3 Supraventricular Extrasystoles => 4 Ventricular Extrasystoles => 5 Atrial Flutter => 6 Right Bundle Branch Block => 7 Left Bundle Branch Block => 8 Left Anterior Hemiblock => 9 Left Posterior Hemiblock => 10 Incomplete Bundle Branch Block => 11 Non-specific Intraventricular Conduction Delay => 12 AV Block First Degree => 13 AV Block Second Degree Type 1 => 14 AV Block Second Degree Type 2 => 15 Right Atrial Hypertrophy => 16 Left Atrial Hypertrophy => 17 Right Ventricular Hypertrophy => 18 Left Ventricular Hypertrophy => 19 ST Segment Elevation => 20 Prolonged QT Interval => 21 Nonspecific T Wave Abnormalities => 22 Other => 99
egeval	select	=> Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4
ecothsp	text	Length (100)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 42 - Visit Date

Visit Date *dd/mm/yyyy*

Annotated eCRF

Variable	**Type**	**Details**
visdat	date	-

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 42 - Clinical Parameters

		Not Done
Weight (kg)		☐

Annotated eCRF

Variable	Type	Details
weight	decimal	Length (4,1)
weightnd	checkbox	1/0 (True/False)

Systolic Blood Pressure (mmHg)		☐	**(33)**

Annotated eCRF

Variable	Type	Details
sysbp	int	Length (3)
sysbpnd	checkbox	1/0 (True/False)
sysbpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diastolic Blood Pressure (mmHg)		☐	**(33)**

Annotated eCRF

Variable	Type	Details
diabp	int	Length (3)
diabpnd	checkbox	1/0 (True/False)
diabpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Heart Rate (beats/min)		☐	**(33)**

Annotated eCRF

Variable	Type	Details
hr	int	Length (3)
hrnd	checkbox	1/0 (True/False)
hrev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diuresis (L/day)

Annotated eCRF

Variable	Type	Details
diuresis	decimal	Length (4,2)

Does the patient show hyperhydratation signs? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
hydrayn	radio	Yes => Y No => N

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 42 - Concomitant Medications

Has there been a change in the concomitant medications? ○ Yes ○ No

Annotated eCRF

Variable	**Type**	**Details**
cmyn1	radio	Yes => Y No => N

If Yes, complete the Previous and Concomitant Medication form

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 42 - Adverse Events

Were there changes in the concomitant diseases or the patient experienced any adverse event? ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
aeyn	radio	Yes => Y No => N

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 42 - Ultrafiltration

1st Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval1	int	Length (5)

2nd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval2	int	Length (5)

3rd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval3	int	Length (5)

Nocturnal Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval4	int	Length (5)

Total ultrafiltration (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagtot	int	Length (5)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 42 - Uric and Lactic Acid

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat2	date	-

	Value	Unit	Low Range	High Range	Not Done	Evaluation
Uric Acid					☐	(33)

Annotated eCRF

Variable	Type	Details
urate_r	decimal	Length (8,2)
urate_u	text	Length (15)
urate_lo	decimal	Length (8,2)
urate_hi	decimal	Length (8,2)
urate_nd	checkbox	1/0 (True/False)
urate_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

	Value	Unit	Low Range	High Range	Not Done	Evaluation
Lactic Acid					☐	(33)

Annotated eCRF

Variable	Type	Details
lacti_r	decimal	Length (8,2)
lacti_u	text	Length (15)
lacti_lo	decimal	Length (8,2)
lacti_hi	decimal	Length (8,2)
lacti_nd	checkbox	1/0 (True/False)
lacti_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Follow-up Period: Day 42 - Hematology

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast	radio	Yes => Y No => N

	Value	Unit	Low Range	High Range	Not Done	Evaluation
RBC count					☐	(33)

Annotated eCRF

Variable	Type	Details
rbc_r	decimal	Length (8,2)
rbc_u	text	Length (15)
rbc_lo	decimal	Length (8,2)
rbc_hi	decimal	Length (8,2)
rbc_nd	checkbox	1/0 (True/False)
rbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Hematocrit					☐	(33)

Annotated eCRF

Variable	Type	Details
hct_r	decimal	Length (8,2)
hct_u	text	Length (15)
hct_lo	decimal	Length (8,2)
hct_hi	decimal	Length (8,2)
hct_nd	checkbox	1/0 (True/False)
hct_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Hemoglobin					☐	(33)

Annotated eCRF

Variable	Type	Details
hgb_r	decimal	Length (8,2)
hgb_u	text	Length (15)
hgb_lo	decimal	Length (8,2)
hgb_hi	decimal	Length (8,2)
hgb_nd	checkbox	1/0 (True/False)
hgb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

WBC					☐	(33)

Annotated eCRF

Variable	Type	Details
wbc_r	decimal	Length (8,2)
wbc_u	text	Length (15)

wbc_lo	decimal	Length (8,2)
wbc_hi	decimal	Length (8,2)
wbc_nd	checkbox	1/0 (True/False)
wbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Neutrophils (33)

Annotated eCRF

Variable	Type	Details
neut_r	decimal	Length (8,2)
neut_u	text	Length (15)
neut_lo	decimal	Length (8,2)
neut_hi	decimal	Length (8,2)
neut_nd	checkbox	1/0 (True/False)
neut_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Basophils (33)

Annotated eCRF

Variable	Type	Details
baso_r	decimal	Length (8,2)
baso_u	text	Length (15)
baso_lo	decimal	Length (8,2)
baso_hi	decimal	Length (8,2)
baso_nd	checkbox	1/0 (True/False)
baso_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Eosinophils (33)

Annotated eCRF

Variable	Type	Details
eos_r	decimal	Length (8,2)
eos_u	text	Length (15)
eos_lo	decimal	Length (8,2)
eos_hi	decimal	Length (8,2)
eos_nd	checkbox	1/0 (True/False)
eos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Lymphocytes (33)

Annotated eCRF

Variable	Type	Details
lym_r	decimal	Length (8,2)
lym_u	text	Length (15)
lym_lo	decimal	Length (8,2)
lym_hi	decimal	Length (8,2)
lym_nd	checkbox	1/0 (True/False)
lym_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Monocytes (33)

Annotated eCRF

Variable	Type	Details
mono_r	decimal	Length (8,2)
mono_u	text	Length (15)
mono_lo	decimal	Length (8,2)
mono_hi	decimal	Length (8,2)
mono_nd	checkbox	1/0 (True/False)
mono_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Platelet count (33)

Annotated eCRF

Variable	Type	Details
plat_r	decimal	Length (8,2)
plat_u	text	Length (15)
plat_lo	decimal	Length (8,2)
plat_hi	decimal	Length (8,2)
plat_nd	checkbox	1/0 (True/False)
plat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Follow-up Period: Day 42 - Clinical Chemistry

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat3	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast1	radio	Yes => Y No => N

	Value	Unit	Low Range	High Range	Not Done	Evaluation
BUN / Azotemia					☐	(33)

Annotated eCRF

Variable	Type	Details
bun_r	decimal	Length (8,2)
bun_u	text	Length (15)
bun_lo	decimal	Length (8,2)
bun_hi	decimal	Length (8,2)
bun_nd	checkbox	1/0 (True/False)
bun_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Creatinine					☐	(33)

Annotated eCRF

Variable	Type	Details
creat_r	decimal	Length (8,2)
creat_u	text	Length (15)
creat_lo	decimal	Length (8,2)
creat_hi	decimal	Length (8,2)
creat_nd	checkbox	1/0 (True/False)
creat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Glucose					☐	(33)

Annotated eCRF

Variable	Type	Details
gluc_r	decimal	Length (8,2)
gluc_u	text	Length (15)
gluc_lo	decimal	Length (8,2)
gluc_hi	decimal	Length (8,2)
gluc_nd	checkbox	1/0 (True/False)
gluc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Cholesterol					☐	(33)

Annotated eCRF

Variable	Type	Details
chol_r	decimal	Length (8,2)
chol_u	text	Length (15)

chol_lo	decimal	Length (8,2)
chol_hi	decimal	Length (8,2)
chol_nd	checkbox	1/0 (True/False)
chol_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

HDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
hdl_r	decimal	Length (8,2)
hdl_u	text	Length (15)
hdl_lo	decimal	Length (8,2)
hdl_hi	decimal	Length (8,2)
hdl_nd	checkbox	1/0 (True/False)
hdl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

LDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
ldl_r	decimal	Length (8,2)
ldl_u	text	Length (15)
ldl_lo	decimal	Length (8,2)
ldl_hi	decimal	Length (8,2)
ldl_nd	checkbox	1/0 (True/False)
ldl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Triglycerides (33)

Annotated eCRF

Variable	Type	Details
trig_r	decimal	Length (8,2)
trig_u	text	Length (15)
trig_lo	decimal	Length (8,2)
trig_hi	decimal	Length (8,2)
trig_nd	checkbox	1/0 (True/False)
trig_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Proteins (33)

Annotated eCRF

Variable	Type	Details
prot_r	decimal	Length (8,2)
prot_u	text	Length (15)
prot_lo	decimal	Length (8,2)
prot_hi	decimal	Length (8,2)
prot_nd	checkbox	1/0 (True/False)
prot_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Albumin (33)

Annotated eCRF

Variable	Type	Details
alb_r	decimal	Length (8,2)
alb_u	text	Length (15)
alb_lo	decimal	Length (8,2)
alb_hi	decimal	Length (8,2)
alb_nd	checkbox	1/0 (True/False)
alb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Bilirubin (33)

Annotated eCRF

Variable	Type	Details
bili_r	decimal	Length (8,2)
bili_u	text	Length (15)
bili_lo	decimal	Length (8,2)
bili_hi	decimal	Length (8,2)
bili_nd	checkbox	1/0 (True/False)
bili_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGOT (AST) (33)

Annotated eCRF

Variable	Type	Details
ast_r	decimal	Length (8,2)
ast_u	text	Length (15)
ast_lo	decimal	Length (8,2)
ast_hi	decimal	Length (8,2)
ast_nd	checkbox	1/0 (True/False)
ast_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGPT (ALT) (33)

Annotated eCRF

Variable	Type	Details
alt_r	decimal	Length (8,2)
alt_u	text	Length (15)
alt_lo	decimal	Length (8,2)
alt_hi	decimal	Length (8,2)
alt_nd	checkbox	1/0 (True/False)
alt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Alkaline Phosphatase (33)

Annotated eCRF

Variable	Type	Details
alp_r	decimal	Length (8,2)
alp_u	text	Length (15)
alp_lo	decimal	Length (8,2)
alp_hi	decimal	Length (8,2)
alp_nd	checkbox	1/0 (True/False)
alp_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

GGT (33)

Annotated eCRF

Variable	Type	Details
ggt_r	decimal	Length (8,2)
ggt_u	text	Length (15)
ggt_lo	decimal	Length (8,2)
ggt_hi	decimal	Length (8,2)
ggt_nd	checkbox	1/0 (True/False)
ggt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Serum Sodium (33)

Annotated eCRF

Variable	Type	Details
sodium_r	decimal	Length (8,2)
sodium_u	text	Length (15)
sodium_lo	decimal	Length (8,2)
sodium_hi	decimal	Length (8,2)
sodium_nd	checkbox	1/0 (True/False)
sodium_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Potassium (33)

Annotated eCRF

Variable	Type	Details
k_r	decimal	Length (8,2)
k_u	text	Length (15)
k_lo	decimal	Length (8,2)
k_hi	decimal	Length (8,2)
k_nd	checkbox	1/0 (True/False)
k_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Calcium (33)

Annotated eCRF

Variable	Type	Details
ca_r	decimal	Length (8,2)
ca_u	text	Length (15)
ca_lo	decimal	Length (8,2)
ca_hi	decimal	Length (8,2)
ca_nd	checkbox	1/0 (True/False)
ca_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Phosphorus (33)

Annotated eCRF

Variable	Type	Details
phos_r	decimal	Length (8,2)
phos_u	text	Length (15)
phos_lo	decimal	Length (8,2)
phos_hi	decimal	Length (8,2)
phos_nd	checkbox	1/0 (True/False)

phos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 56 - Visit Date

Visit Date *dd/mm/yyyy*

Annotated eCRF

Variable	**Type**	**Details**
visdat	date	-

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 56 - Clinical Parameters

		Not Done
Weight (kg)		☐

Annotated eCRF

Variable	**Type**	**Details**
weight	decimal	Length (4,1)
weightnd	checkbox	1/0 (True/False)

Systolic Blood Pressure (mmHg)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
sysbp	int	Length (3)
sysbpnd	checkbox	1/0 (True/False)
sysbpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diastolic Blood Pressure (mmHg)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
diabp	int	Length (3)
diabpnd	checkbox	1/0 (True/False)
diabpev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Heart Rate (beats/min)		☐		**(33)**

Annotated eCRF

Variable	**Type**	**Details**
hr	int	Length (3)
hrnd	checkbox	1/0 (True/False)
hrev	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Diuresis (L/day)

Annotated eCRF

Variable	**Type**	**Details**
diuresis	decimal	Length (4,2)

Does the patient show hyperhydratation signs? ○ Yes ○ No

Annotated eCRF

Variable	**Type**	**Details**
hydrayn	radio	Yes => Y No => N

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 56 - Concomitant Medications

Has there been a change in the concomitant medications? ○ Yes ○ No

Annotated eCRF

Variable	**Type**	**Details**
cmyn1	radio	Yes => Y No => N

If Yes, complete the Previous and Concomitant Medication form

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 56 - Adverse Events

Were there changes in the concomitant diseases or the patient experienced any adverse event? ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
aeyn	radio	Yes => Y No => N

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 56 - Subjective Questionnaire

Did the patient fill in the subjective questionnaire ○ Yes ○ No

		Annotated eCRF
Variable	**Type**	**Details**
qsyn	radio	Yes => Y No => N

Total Score

		Annotated eCRF
Variable	**Type**	**Details**
qstot	int	Length (3)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 56 - Weekly Total Urea Kt/V

Total Urea Kt/V (/week)

Annotated eCRF

Variable	**Type**	**Details**
ureaval	decimal	Length (8,2)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code **Randomization Code**

Follow-up Period: Day 56 - Peritoneal Equilibration Test (PET)

Dialysate/Plasma Creatinine

Annotated eCRF

Variable	Type	Details
petval	decimal	Length (8,2)

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 56 - Weekly Total Creatine Clearance

Creatine Clearance (/week)

Annotated eCRF

Variable	**Type**	**Details**
creatval	decimal	Length (8,2)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 56 - Ultrafiltration

1st Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval1	int	Length (5)

2nd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval2	int	Length (5)

3rd Daily Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval3	int	Length (5)

Nocturnal Bag (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagval4	int	Length (5)

Total ultrafiltration (mL)

		Annotated eCRF
Variable	**Type**	**Details**
bagtot	int	Length (5)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 56 - CA 125

CA 125 (U.a./mL)

Annotated eCRF

Variable	**Type**	**Details**
ca125val	decimal	Length (8,1)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 56 - Proteins in Ultrafiltration

Proteins in ultrafiltration (g/dL)

Annotated eCRF

Variable	**Type**	**Details**
protval	decimal	Length (8,1)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Follow-up Period: Day 56 - Uric and Lactic Acid

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat2	date	-

Value	Unit	Low Range	High Range	Not Done	Evaluation
Uric Acid				☐	(33)

Annotated eCRF

Variable	Type	Details
urate_r	decimal	Length (8,2)
urate_u	text	Length (15)
urate_lo	decimal	Length (8,2)
urate_hi	decimal	Length (8,2)
urate_nd	checkbox	1/0 (True/False)
urate_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Value	Unit	Low Range	High Range	Not Done	Evaluation
Lactic Acid				☐	(33)

Annotated eCRF

Variable	Type	Details
lacti_r	decimal	Length (8,2)
lacti_u	text	Length (15)
lacti_lo	decimal	Length (8,2)
lacti_hi	decimal	Length (8,2)
lacti_nd	checkbox	1/0 (True/False)
lacti_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Follow-up Period: Day 56 - Hematology

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast	radio	Yes => Y No => N

	Value	Unit	Low Range	High Range	Not Done	Evaluation
RBC count					☐	(33)

Annotated eCRF

Variable	Type	Details
rbc_r	decimal	Length (8,2)
rbc_u	text	Length (15)
rbc_lo	decimal	Length (8,2)
rbc_hi	decimal	Length (8,2)
rbc_nd	checkbox	1/0 (True/False)
rbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Hematocrit					☐	(33)

Annotated eCRF

Variable	Type	Details
hct_r	decimal	Length (8,2)
hct_u	text	Length (15)
hct_lo	decimal	Length (8,2)
hct_hi	decimal	Length (8,2)
hct_nd	checkbox	1/0 (True/False)
hct_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Hemoglobin					☐	(33)

Annotated eCRF

Variable	Type	Details
hgb_r	decimal	Length (8,2)
hgb_u	text	Length (15)
hgb_lo	decimal	Length (8,2)
hgb_hi	decimal	Length (8,2)
hgb_nd	checkbox	1/0 (True/False)
hgb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

WBC					☐	(33)

Annotated eCRF

Variable	Type	Details
wbc_r	decimal	Length (8,2)
wbc_u	text	Length (15)

wbc_lo	decimal	Length (8,2)
wbc_hi	decimal	Length (8,2)
wbc_nd	checkbox	1/0 (True/False)
wbc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Neutrophils (33)

Annotated eCRF

Variable	Type	Details
neut_r	decimal	Length (8,2)
neut_u	text	Length (15)
neut_lo	decimal	Length (8,2)
neut_hi	decimal	Length (8,2)
neut_nd	checkbox	1/0 (True/False)
neut_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Basophils (33)

Annotated eCRF

Variable	Type	Details
baso_r	decimal	Length (8,2)
baso_u	text	Length (15)
baso_lo	decimal	Length (8,2)
baso_hi	decimal	Length (8,2)
baso_nd	checkbox	1/0 (True/False)
baso_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Eosinophils (33)

Annotated eCRF

Variable	Type	Details
eos_r	decimal	Length (8,2)
eos_u	text	Length (15)
eos_lo	decimal	Length (8,2)
eos_hi	decimal	Length (8,2)
eos_nd	checkbox	1/0 (True/False)
eos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Lymphocytes (33)

Annotated eCRF

Variable	Type	Details
lym_r	decimal	Length (8,2)
lym_u	text	Length (15)
lym_lo	decimal	Length (8,2)
lym_hi	decimal	Length (8,2)
lym_nd	checkbox	1/0 (True/False)
lym_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Monocytes (33)

Annotated eCRF

Variable	Type	Details
mono_r	decimal	Length (8,2)
mono_u	text	Length (15)
mono_lo	decimal	Length (8,2)
mono_hi	decimal	Length (8,2)
mono_nd	checkbox	1/0 (True/False)
mono_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Platelet count						**(33)**

Annotated eCRF

Variable	Type	Details
plat_r	decimal	Length (8,2)
plat_u	text	Length (15)
plat_lo	decimal	Length (8,2)
plat_hi	decimal	Length (8,2)
plat_nd	checkbox	1/0 (True/False)
plat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		Randomization Code	

Follow-up Period: Day 56 - Clinical Chemistry

Sample collection date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
lbdat3	date	-

Was the patient fasting? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
lbfast1	radio	Yes => Y No => N

	Value	Unit	Low Range	High Range	Not Done	Evaluation
BUN / Azotemia					☐	(33)

Annotated eCRF

Variable	Type	Details
bun_r	decimal	Length (8,2)
bun_u	text	Length (15)
bun_lo	decimal	Length (8,2)
bun_hi	decimal	Length (8,2)
bun_nd	checkbox	1/0 (True/False)
bun_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Creatinine					☐	(33)

Annotated eCRF

Variable	Type	Details
creat_r	decimal	Length (8,2)
creat_u	text	Length (15)
creat_lo	decimal	Length (8,2)
creat_hi	decimal	Length (8,2)
creat_nd	checkbox	1/0 (True/False)
creat_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Glucose					☐	(33)

Annotated eCRF

Variable	Type	Details
gluc_r	decimal	Length (8,2)
gluc_u	text	Length (15)
gluc_lo	decimal	Length (8,2)
gluc_hi	decimal	Length (8,2)
gluc_nd	checkbox	1/0 (True/False)
gluc_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Cholesterol					☐	(33)

Annotated eCRF

Variable	Type	Details
chol_r	decimal	Length (8,2)
chol_u	text	Length (15)

chol_lo	decimal	Length (8,2)
chol_hi	decimal	Length (8,2)
chol_nd	checkbox	1/0 (True/False)
chol_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

HDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
hdl_r	decimal	Length (8,2)
hdl_u	text	Length (15)
hdl_lo	decimal	Length (8,2)
hdl_hi	decimal	Length (8,2)
hdl_nd	checkbox	1/0 (True/False)
hdl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

LDL Cholesterol (33)

Annotated eCRF

Variable	Type	Details
ldl_r	decimal	Length (8,2)
ldl_u	text	Length (15)
ldl_lo	decimal	Length (8,2)
ldl_hi	decimal	Length (8,2)
ldl_nd	checkbox	1/0 (True/False)
ldl_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Triglycerides (33)

Annotated eCRF

Variable	Type	Details
trig_r	decimal	Length (8,2)
trig_u	text	Length (15)
trig_lo	decimal	Length (8,2)
trig_hi	decimal	Length (8,2)
trig_nd	checkbox	1/0 (True/False)
trig_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Proteins (33)

Annotated eCRF

Variable	Type	Details
prot_r	decimal	Length (8,2)
prot_u	text	Length (15)
prot_lo	decimal	Length (8,2)
prot_hi	decimal	Length (8,2)
prot_nd	checkbox	1/0 (True/False)
prot_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Albumin (33)

Annotated eCRF

Variable	Type	Details
alb_r	decimal	Length (8,2)
alb_u	text	Length (15)
alb_lo	decimal	Length (8,2)
alb_hi	decimal	Length (8,2)
alb_nd	checkbox	1/0 (True/False)
alb_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Total Bilirubin (33)

Annotated eCRF

Variable	Type	Details
bili_r	decimal	Length (8,2)
bili_u	text	Length (15)
bili_lo	decimal	Length (8,2)
bili_hi	decimal	Length (8,2)
bili_nd	checkbox	1/0 (True/False)
bili_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGOT (AST) (33)

Annotated eCRF

Variable	Type	Details
ast_r	decimal	Length (8,2)
ast_u	text	Length (15)
ast_lo	decimal	Length (8,2)
ast_hi	decimal	Length (8,2)
ast_nd	checkbox	1/0 (True/False)
ast_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

SGPT (ALT) (33)

Annotated eCRF

Variable	Type	Details
alt_r	decimal	Length (8,2)
alt_u	text	Length (15)
alt_lo	decimal	Length (8,2)
alt_hi	decimal	Length (8,2)
alt_nd	checkbox	1/0 (True/False)
alt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Alkaline Phosphatase (33)

Annotated eCRF

Variable	Type	Details
alp_r	decimal	Length (8,2)
alp_u	text	Length (15)
alp_lo	decimal	Length (8,2)
alp_hi	decimal	Length (8,2)
alp_nd	checkbox	1/0 (True/False)
alp_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

GGT (33)

Annotated eCRF

Variable	Type	Details
ggt_r	decimal	Length (8,2)
ggt_u	text	Length (15)
ggt_lo	decimal	Length (8,2)
ggt_hi	decimal	Length (8,2)
ggt_nd	checkbox	1/0 (True/False)
ggt_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Serum Sodium (33)

Annotated eCRF

Variable	Type	Details
sodium_r	decimal	Length (8,2)
sodium_u	text	Length (15)
sodium_lo	decimal	Length (8,2)
sodium_hi	decimal	Length (8,2)
sodium_nd	checkbox	1/0 (True/False)
sodium_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Potassium (33)

Annotated eCRF

Variable	Type	Details
k_r	decimal	Length (8,2)
k_u	text	Length (15)
k_lo	decimal	Length (8,2)
k_hi	decimal	Length (8,2)
k_nd	checkbox	1/0 (True/False)
k_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Calcium (33)

Annotated eCRF

Variable	Type	Details
ca_r	decimal	Length (8,2)
ca_u	text	Length (15)
ca_lo	decimal	Length (8,2)
ca_hi	decimal	Length (8,2)
ca_nd	checkbox	1/0 (True/False)
ca_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Phosphorus (33)

Annotated eCRF

Variable	Type	Details
phos_r	decimal	Length (8,2)
phos_u	text	Length (15)
phos_lo	decimal	Length (8,2)
phos_hi	decimal	Length (8,2)
phos_nd	checkbox	1/0 (True/False)

phos_e	select	=> Normal => 1 Not Clinically Significant => 2 Clinically significant for concomitant disease => 3 Clinically significant for the pathology under study => 4

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

End of Study

End of Study Date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
ltvisdat	date	-

Did the patient complete the study according to the protocol ? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
dsyn	radio	Yes => Y No => N

Did the patient complete treatment? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
comptryn	radio	Yes => Y No => N

If NO, Date of last treatment *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
exendat	date	-

Principal Reason for Subject Premature discontinuation **(30)**

Annotated eCRF

Variable	Type	Details
dsdecod	select	=> Adverse Event => 1 Death => 2 Pregnancy => 3 Withdrawal of consent => 4 Initiation of disallowed concomitant therapy => 5 Inclusion/Exclusion criteria not fulfilled => 6 Changes of the patient's clinical condition => 7 Patient's Non compliance => 8 Lost to follow-up => 9 Other => 10

AE N

Annotated eCRF

Variable	Type	Details
aspid	int	Length (3)

Date of death *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
deadat	date	-

Was death reported as AE? ○ Yes ○ No

Annotated eCRF

Variable	Type	Details
deathyn	radio	Yes => Y No => N

if YES, please specify AE N.

Annotated eCRF

Variable	Type	Details
aeseq	int	Length (3)

if NO, specify primary cause

Annotated eCRF

Variable	Type	Details
cause	text	Length (100)

Specify

Annotated eCRF

Variable	Type	Details
dsterm	textarea	-

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Previous and Concomitant Medication - Previous and Concomitant Medication

Medication (trade name)

Annotated eCRF

Variable	**Type**	**Details**
cmtrt	text	Length (50)

Start Date *na/na/na*

Annotated eCRF

Variable	**Type**	**Details**
cmstdat	partial_date_ymd	-

Stop Date *na/na/na*

Annotated eCRF

Variable	**Type**	**Details**
cmendat	partial_date_ymd	-

ongoing ☐

Annotated eCRF

Variable	**Type**	**Details**
cmongo	checkbox	1/0 (True/False)

Total daily Dose

Annotated eCRF

Variable	**Type**	**Details**
cmdostot	text	Length (15)

Unit

Annotated eCRF

Variable	**Type**	**Details**
cmdosu	text	Length (15)

Frequency **(28)**

Annotated eCRF

Variable	**Type**	**Details**
cmfreq	select	=> ONCE => ONCE Daily => QD Twice a day => BID 3 Times per Day => TID 4 Times per Day => QID Every other Day => QOD Every 4 Hours => Q4H Every 6 Hours => Q6H Every 8 Hours => Q8H Every 12 Hours => Q12H As Needed => PRN Unknown => UNK Other => OTH

Route **(29)**

Annotated eCRF

Variable	**Type**	**Details**
cmroute	select	=> Intravenous => IV Oral => PO Intramuscular => IM Inhalation => INH Rectal => RECTAL Topical => TOP Nasal => NAS Subcutaneous => SC Sublingual => SB Transdermal => TD Ophthalmic => OPH Parenteral => PAR Auricular => OTIC Vaginal => VAG Unknown => UNK Other => OTH

Indication

Annotated eCRF

Variable	Type	Details
cmindc	text	Length (100)

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Adverse Events - ae

N.

Annotated eCRF

Variable	Type	Details
aespid	int	Length (3)

Adverse Event

Annotated eCRF

Variable	Type	Details
aeterm	text	Length (100)

Start Date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
aestdat	date	-

Stop Date *dd/mm/yyyy*

Annotated eCRF

Variable	Type	Details
aeendat	date	-

Not Serious ☐

Annotated eCRF

Variable	Type	Details
aesno	checkbox	1/0 (True/False)

Death ☐

Annotated eCRF

Variable	Type	Details
aestdh	checkbox	1/0 (True/False)

Life-threatening ☐

Annotated eCRF

Variable	Type	Details
aeslife	checkbox	1/0 (True/False)

Hospitalization or prolongation of existing inpatients' hospitalization ☐

Annotated eCRF

Variable	Type	Details
aeshosp	checkbox	1/0 (True/False)

Persistent or significant disability or incapacity ☐

Annotated eCRF

Variable	Type	Details
aesdisab	checkbox	1/0 (True/False)

Congenital anomaly or birth defect ☐

Annotated eCRF

Variable	Type	Details
aescong	checkbox	1/0 (True/False)

Other Medical Condition ☐

Annotated eCRF

Variable	Type	Details
aesmie	checkbox	1/0 (True/False)

Intensity ○ Mild ○ Moderate ○ Severe

Annotated eCRF

Variable	Type	Details
aesev	radio	Mild => Mild Moderate => Moderate Severe => Severe

Relationship to Study Drug ○ Definitely related ○ Probably related ○ Possibly related ○ Unlikely related ○ Not related

Annotated eCRF		
Variable	**Type**	**Details**
aerel	radio	Definitely related => 1 Probably related => 2 Possibly related => 3 Unlikely related => 4 Not related => 5

None ☐

Annotated eCRF		
Variable	**Type**	**Details**
aeacn01	checkbox	1/0 (True/False)

Study drug interrupted and restarted ☐

Annotated eCRF		
Variable	**Type**	**Details**
aeacn02	checkbox	1/0 (True/False)

Dose reduced ☐

Annotated eCRF		
Variable	**Type**	**Details**
aeacn03	checkbox	1/0 (True/False)

Study Drug Discontinued ☐

Annotated eCRF		
Variable	**Type**	**Details**
aeacn04	checkbox	1/0 (True/False)

Specific therapy/medication ☐

Annotated eCRF		
Variable	**Type**	**Details**
aeacn05	checkbox	1/0 (True/False)

Hospitalization ☐

Annotated eCRF		
Variable	**Type**	**Details**
aeacn06	checkbox	1/0 (True/False)

Outcome ○ Recovered ○ Recovered with sequelae ○ Not recovered ○ Death ○ Unknown

Annotated eCRF		
Variable	**Type**	**Details**
aeout	radio	Recovered => 1 Recovered with sequelae => 2 Not recovered => 3 Death => 4 Unknown => 5

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Bag Accountability

	Bags for the patient	**Bags used by the patient**	**Bags used by the patient**
Day 0 - Day 14			

Annotated eCRF

Variable	**Type**	**Details**
dispamt1	int	Length (3)
usamt1	int	Length (3)
retamt1	int	Length (3)

Day 14 - Day 28			

Annotated eCRF

Variable	**Type**	**Details**
dispamt2	int	Length (3)
usamt2	int	Length (3)
retamt2	int	Length (3)

Signed by		**Date**	

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code **Randomization Code**

Peritoneal Equilibration Test (PET) Glucose - PET Glucose

	Screening Period: Day 0	Not Done	Intervention Period: Day 28	Not Done	Follow-up Period: Day 56	Not Done
Peritoneal Equilibration Test (PET)		☐		☐		☐

Annotated eCRF

Variable	Type	Details
petgluc_t0	decimal	Length (8,2)
petgluc_t0_nd	checkbox	1/0 (True/False)
petgluc_t28	decimal	Length (8,2)
petgluc_t28_nd	checkbox	1/0 (True/False)
petglucd_t56	decimal	Length (8,2)
petgluc_t56_nd	checkbox	1/0 (True/False)

Signed by **Date**

ACTide Ip00109 - Annotated eCRF **[Version: 2.0.1 Build: 1]**

Patient Code		**Randomization Code**	

Index - Select Values

(28)	; ONCE; Daily; Twice a day; 3 Times per Day; 4 Times per Day; Every other Day; Every 4 Hours; Every 6 Hours; Every 8 Hours; Every 12 Hours; As Needed; Unknown; Other
(29)	; Intravenous; Oral; Intramuscular; Inhalation; Rectal; Topical; Nasal; Subcutaneous; Sublingual; Transdermal; Ophthalmic; Parenteral; Auricular; Vaginal; Unknown; Other
(30)	; Adverse Event; Death; Pregnancy; Withdrawal of consent; Initiation of disallowed concomitant therapy; Inclusion/Exclusion criteria not fulfilled; Changes of the patient’s clinical condition; Patient’s Non compliance; Lost to follow-up; Other
(31)	; Not Clinically Significant; Clinically significant for concomitant disease; Clinically significant for the pathology under study
(32)	; Sinus Arrhythmia; Sinus Bradycardia; Sinus Tachycardia; Supraventricular Extrasystoles; Ventricular Extrasystoles; Atrial Flutter; Right Bundle Branch Block; Left Bundle Branch Block; Left Anterior Hemiblock; Left Posterior Hemiblock; Incomplete Bundle Branch Block; Non-specific Intraventricular Conduction Delay; AV Block First Degree; AV Block Second Degree Type 1; AV Block Second Degree Type 2; Right Atrial Hypertrophy; Left Atrial Hypertrophy; Right Ventricular Hypertrophy; Left Ventricular Hypertrophy; ST Segment Elevation; Prolonged QT Interval; Nonspecific T Wave Abnormalities; Other
(33)	; Normal; Not Clinically Significant; Clinically significant for concomitant disease; Clinically significant for the pathology under study
(34)	; Eyes; Ears, Nose, Throat; Head and Neck; Cardiovascular; Lungs; Abdomen; Musculoskeletal; Lymph nodes ; Skin; Urogenital System; Nervous System; Mental State; Other

Signed by		**Date**	

16.1.3 Independent Ethical Committee/IRB and Sample Informed Consents

Table 16.1.3.1 Independent Ethical Committee

Investigators	Name and Address of IEC
BONOMINI Prof. Mario	Ethics Committee of University G. d'Annunzio of Chieti-Pescara Address: Via dei Vestini, 31, 66013 Chieti Scalo
GESUALDO Prof Loreto	Comitato Etico Interregionale c/o Policlinico di Bari Address: Piazza G. Cesare 11, 70124 Bari
GRANDALIANO Prof Giuseppe	Ethical Committee Policlinico Agostino Gemelli Address: Segreteria tecnico scientifica, ex Collegio Ioanneum, stanza 221, Largo F. Vito, 1, 00168 Roma

16.1.3.2 Sample Consent Forms

Table 16.1.3.2.1 History of ICF modifications

TITLE	VERSION	DATE	COMMENTS
INFORMATION SHEET AND INFORMED CONSENT FOR PATIENT'S PARENTS	English Master Version	19/03/2020	Based on the Study Protocol Amendment 2 dated March 19th, 2020
INFORMATION SHEET AND INFORMED CONSENT FORM FOR ADULT PATIENTS	English Master Version	19/03/2020	Based on the Study Protocol Amendment 2 dated March 19th, 2020
INFORMATION SHEET AND INFORMED CONSENT FOR PATIENT'S PARENTS	English Master Version	15/10/2018	Based on the Study Protocol Amendment 1 dated October 15th, 2018
INFORMATION SHEET AND INFORMED CONSENT FORM FOR ADULT PATIENTS	English Master Version	15/10/2018	Based on the Study Protocol Amendment 1 dated October 15th, 2018
INFORMATION SHEET AND INFORMED CONSENT FORM FOR ADULT PATIENTS	English Master Version	25/01/2017	Based on the Study Protocol dated November 28th, 2016
INFORMATION SHEET AND INFORMED CONSENT FOR PATIENT'S PARENTS	English Master Version	09/01/2017	Based on the Study Protocol dated November 28th, 2016

The written information for patient and sample Consent Forms included in this Appendix are the templates developed for the study and were also translated in foreign languages according to the participating sites.

The foreign language documents are on file at AryoGen Pharmed and are available upon request.

Information Sheet and Informed Consent Form for patient's parents

Study title: A RANDOMIZED, MULTICENTER, DOUBLE BLIND CLINICAL TRIAL COMPARING PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY OF A BIOSIMILAR EPTACOG ALFA (AryoSeven) AND NOVOSEVEN®, IN PATIENTS WITH HAEMOPHILIA A OR B WITH INHIBITORS.

Protocol Identifier: UGA 2014-01

Dear Parents,

We are inviting you to let your son to take part in a clinical trial, a type of research study, because your son has haemophilia A or B .
Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Take time to decide whether or not you wish to take part. You may discuss your possible participation in the study and alternative treatments with your family or any doctor.

The study doctor will give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

Maybe you do not understand some words. Please ask the study doctor to stop as you go through the information and the study doctor will take time to explain. If you have questions later, you can ask the study doctor or the staff.

AIM OF THE STUDY

This clinical trial is a comparative study between efficacy of recombinant activated factor VII produced by the Sponsor of the study, AryoGen Pharmed Company (AryoSeven™) and NovoSeven®.

It is expected that at least 50 patients will take part in this research from various haemophilia centers in different Countries participating in this clinical trial.

We are doing this study to further complete the documentation on the product biosimilar eptacog alfa AryoSeven™. The aim of this study is to show that AryoSeven™ is similar to NovoSeven® .

INFORMATION ON THE TRIAL DRUG "AryoSeven™"

AryoGen biosimilar eptacog alfa (activated) is a biosimilar version of NovoSeven® (Novo Nordisk) which is the Reference Medicinal Product (RMP).

The ARYOGEN biosimilar eptacog alfa is already marketed in Iran with the trade name AryoSeven.

The Company obtained advice from the European Medicine Agency (EMA) on 23 July 2015 and 15 September 2016 on questions concerning quality development, pre-clinical development and clinical development for obtaining Marketing Authorization in Europe.

Eptacog alfa, activated [activated recombinant human coagulation Factor VII (rFVIIa)] is structurally similar to human plasma-derived coagulation factor VIIa .This vitamin K-dependent glycoprotein is promoting hemostasis at the site of bleeding when the coagulation factors do not work correctly.

Eptacog alfa, activated is a replacement therapy that has changed the management of bleeding in patients with congenital disorders of coagulation, such as Haemophilia A/B with inhibitors, Congenital factor VII (FVII) deficiency and Glanzmann thromboasthenia.

Although therapeutic advances in control of bleeding episodes have led to a decreased morbidity and a better quality of life, the cost of treatment limits its access. This led to the development of a biosimilar version of of NovoSeven.

STUDY DESIGN

If disease and conditions of your child satisfy study inclusion criteria, you will be asked to sign the consent of study participation before any investigation is performed.

If you decide to let your son to participate and sign the Informed Consent form, your child will undergo to a full medical screening and to the following investigations.

At Screening visit, visit 1, your son will be assessed for inclusion and exclusion criteria and blood sampling for routine laboratory assessment of immunogenicity (presence of anti-Factor VII antibody screening) will be obtained. This testing will be done at local laboratory. Screened patients will be enrolled if the results of antibodies assessed by the study local lab will be negative (samples will be stored and sent to the central lab (ERBC, Pomezia – Roma – Italy) later, for confirmation.

As soon as laboratory (local lab) results for immunogenicity will be available, your child will be scheduled for two dosing visits (visits 2 and 3) separated by a period of at least 3 days.

According to this type of study, he will be randomized (i.e, assigned by chance) to receive at visit 2 and 3 either a indistinguishable single therapeutic dose of NovoSeven® and one single dose of AryoSeven™, or vice versa, with doses at distance of three (3) days (this phase of the study is called “PK cross over and immunogenicity follow-up group”). NovoSeven and AryoSeven are similar drugs.
Patients will be hospitalized at time of study medication administration and plasma sampling.

Your son will receive the product with undistinguishable syringes that is in double blinding (masking, by an independent operator). This means that the kind of medicine is kept masked from both the Doctors participating in this study and the Patient.

The assignment to a product or to the other will occur randomly (casually, by chance) accordingly to a randomization list generated by a computer.
At visit 2 and 3, your child will be hospitalized and blood sampling will be taken several time during the 24 hours: 10 min- prior to dose administration and at 10 min, 20 min, 1 h, 3 h, 5 h, 8 h, 12 h, 24 h and 30 h after AryoSeven or NovoSeven injection.
From the arm not used for rFVIIa infusion, 5 ml of blood will be drawn during the each sampling . For bioanalytical reasons, 9 ml of blood, instead of 5ml, will be drawn during the Visit 2 and Visit 3 at the timepoints1h and 12h only.
.

At the end of this phase, your son will be followed by the Doctors participating in this study for 12 months (this phase of the study is called “Immunogenicity Open follow up phase”), with periodic controls every 3 months for 1 year (4 visits) for blood sampling for determination of antibody formation (immunogenicity) monitoring.

During this period, your son will be treated with AryoSeven™ in Hospital, every time a bleeding should happen, with dose, frequency and duration of treatment that will be based on the Investigator’s decision, with the aim of monitoring inhibiting antibody formation, lack of efficacy and study adverse events. Treatment with AryoSeven should be given at home (study medication supplied by the study center), with dose and duration of treatment based on the Investigator’s decision, and intravenous self-injection by the parent/caregiver/support person.
Your son should receive AryoSeven for prevention (prophylaxis) of bleeding, with dose and duration of treatment that will be based on the Investigator’s decision

The modality of treatment with AryoSeven will be decided by the Investigator.

Blood sampling will be taken every 3 months.

Samples of all Patients will be periodically shipped from the study center laboratory to the central laboratory for confirmatory analysis.

Assessment of biochemistry, hematology and coagulation-related parameters will be performed at screening (visit 1), pre-dosing at visit 2 and 3, and every 3 months in the follow up period of 12 months.

You will be asked to provide information on your child primary disease and disease status, medical history, past and current concomitant diseases and treatments, demographic data, baseline characteristics: age, sex, baseline weight, height, race and surgical history, CNS function at study entry, physical examination findings.

You should contact the study doctor or site staff for any additional clarifications or if you experience any change in the way your son/daughter feels following administration of the study drug.

Simultaneous use of prothrombin complex concentrates, activated or not – or – plasma, is NOT permitted.

Patients may NOT be treated concurrently with rFXIII medications.

Experience with concomitant administration of anti-fibrinolytics is limited and concomitant treatment with these products should be avoided.

POTENTIAL BENEFITS AND RISKS TO PARTICIPATE

The medicine (AryoSeven™) has shown similarity with the branded product (NovoSeven®) in all of previous laboratory and clinical researches. Also method of administration and dosage of this medicine are quite similar to branded product.

ARYOGEN biosimilar eptaco alfa (AryoSeven) has been studied in a multicenter randomized, controlled, double blind clinical trial with 66 patients with congenital factor VII deficiency (31 patients randomized to AryoSeven; 35 patients randomized to NovoSeven). There were no withdrawals due to adverse events, death, serious adverse events, or adverse events evaluated by the investigators as possibly or probably related to study medications. No serious adverse events have been observed during the study period and the 3 months follow up. The numbers and types of adverse events were comparable with no significant difference between the two Arms.

However, this medicine like any other medicines may have side effects, all of patients are under full insurance coverage by AryoGen Pharmed Company for these possible side effects and all of treatment costs are covered by AryoGen Pharmed Co.

The common Adverse Events observed in controlled and uncontrolled studies in patients that received AryoSeven or NovoSeven were: Headache, Nausea/Vomiting, Fever, Allergic, Leg pain, Chest pain, Arthralgia, Cyanosis, Pruritus, Dizziness, Hypoaesthesia, Rash, Infusion site rash, Urticaria and Hypotension.

We cannot ensure that your child will personally benefit from participating in this study. However, by taking part in this study you may contribute with new information that may benefit patients with haemophilia A/B with inhibitor in the future.

STUDY COST

Pharmaceutical products as well as diagnostic and therapeutic procedures are free for patients participating in the study and transportation costs will be compensated for them.

CONFIDENTIALITY

All data collected by this study will be used under legal standards. Data will be stored and processed anonymously i.e. your child's data will not be identified by the patient name but only by a patient number. This means that only anonymous data will be transmitted. Patient identity and anonymity will be treated as strictly confidential also in the case of a publication of the study results.

Representatives of the Sponsor or of the authorized Clinical Research Organization conducting the study and/or representatives of the responsible national health authorities will have the right to access medical data and to review study procedure without breaking of anonymity of study participants under the legal regulations. These inspections are performed for reasons of safety and reliability of the data. All persons involved are subject to a strict confidentiality agreement.

By signing this Informed Consent Form, your authorization and permission are given to the above mentioned representatives to access your medical records for the fulfillment of this study and for the processing of your child personal data, as well as the transfer of such data outside your Country for the purposes of this clinical study, in accordance with the terms and mechanisms provided in this information sheet.

In accordance with the applicable local regulations and the General Data Protection Regulation (GDPR) n 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, the authorized Clinical Research Organization, Sintesi Research S.r.l., will treat your child personal data exclusively to improve experimentation and for purposes of Pharmacovigilance. In carrying out this task the parties will not go beyond their respective competences and will comply with the requirements deriving from Good Clinical Practice.

All personal information will remain confidential and it will be only used for statistical analysis by the research team.

STUDY PARTICIPATION

The Participation in this study is based completely on free will and you are free to withdraw your consent whenever you decide, without having to give a reason for doing so and without subjecting your child to any disadvantages or prejudices.

If, after accepting initially to enter into the study, you decide your child should not participate in the study any longer, you may withdraw your consent and your doctor will switch your child to an alternative treatment among those available.

The decision to not participate in this study or to interrupt the participation at any time during the study will have no influence whatsoever on the quality of treatment your child will get from your doctor.

The sponsor or your doctor may terminate the participation of your child in the study if it is in the interest of his/her health to do so or should new information arise during the course of the study which could put his/her safety at risk.

INSURANCE

In case your child should experience any damage caused by the study treatment, he/she will receive adequate care and assistance without any expense for you.

This study is covered by Insurance Policy nr. _____stipulated by the Sponsor with the Insurance Company _____that will cover for any eventual damage to your child's health derived from study participation.

CONTACT INFORMATION

If you have any other additional questions concerning the study medication and protocol please contact your doctor _____ (name and surname) personally or by phone at the number _____ (telephone number).

Informed Consent Form for Patient's Parents

Study title: A RANDOMIZED, MULTICENTER, DOUBLE BLIND CLINICAL TRIAL COMPARING PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY OF A BIOSIMILAR EPTACOG ALFA (AryoSeven) AND NOVOSEVEN®, IN PATIENTS WITH HAEMOPHILIA A OR B WITH INHIBITORS. UGA 2014-01

We, the parents of, _____

- We confirm that the study Doctor (Investigator) explained us the study, We read and understood this information sheet on (date) _____ and we had the opportunity to ask our questions.
- The study Doctor informed us of the risk and possible benefits associated with the participation in this study.
- We know that the participation of our child in this study is voluntary and We can withdraw freely at any time without giving a reason and also his/her medical care or legal rights will not be affected.
- We authorize the study coordinator and his team involved in the study, the Sponsor of the study, the Medical Ethics Committee, the Office of Drug Supervision in MOH and any other Health Authority that need to inspect this study to observe my child's health records any time, during the study or later if any further investigation may be conducted related to this study (even if We withdraw from the study I agree with the access).
- However, We have been informed that the medical information of our son/daughter will not be disclosed and such data will only be used for statistical purposes.
- We agree to participate in this study.
- We have received a signed copy of this Informed Consent for my information.

_____

Mother / guardian Name (capital letters)

_____ _____

Mother / guardian Signature Date

_____

Father / guardian name (Capital letters)

_____ _____

Father / guardian Signature Date

Investigator's Statement and Signature

I, the undersigned Dr. ..... , testify that Mr/Ms. ....., on reading the attached Information Sheet responded to all questions and signed his/her consent to participate in this Study, had clearly understood the information received and was capable of arriving at a fully informed choice.

I hereby declare that I have explained the above study and certify that to the best of my knowledge the subject signing this consent form understands the nature, demands, potential risks and benefits involved in participating in this study.

_____

Investigator's name (Capital letters)

_____ _____

Investigator's Signature Date

Note: one copy of this signed and dated Informed Consent form will be given to me for my records and future reference and original will be placed in the subject's file.

Information Sheet and Informed Consent Form for Adult Patients

Study title: A RANDOMIZED, MULTICENTER, DOUBLE BLIND CLINICAL TRIAL COMPARING PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY OF A BIOSIMILAR EPTACOG ALFA (AryoSeven) AND NOVOSEVEN®, IN PATIENTS WITH HAEMOPHILIA A OR B WITH INHIBITORS

Protocol Identifier: UGA 2014-01

Dear Patient,

We are inviting you to take part in a clinical trial, a type of research study, because you have Hemophilia A/B with inhibitor titer.
Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Take time to decide whether or not you wish to take part. You may discuss your possible participation in the study and alternative treatments with your family or any doctor.

The study doctor will give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

Maybe you do not understand some words. Please ask the study doctor to stop as you go through the information and the study doctor will take time to explain. If you have questions later, you can ask the study doctor or the staff.

AIM OF THE STUDY

This clinical trial is a comparative study between efficacy of recombinant activated factor VII produced by the Sponsor of the study, AryoGen Pharmed Company (AryoSeven™) and NovoSeven®.

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AryoGen biosimilar eptacog alfa (activated) is a biosimilar version of NovoSeven® (Novo Nordisk) which is the Reference Medicinal Product (RMP).

The ARYOGEN biosimilar eptacog alfa is already marketed in Iran with the trade name

AryoSeven.

The Company obtained advice from the European Medicine Agency (EMA) on 23 July 2015 and 15 September 2016 on questions concerning quality development, pre-clinical development and clinical development for obtaining Marketing Authorization in Europe.

Eptacog alfa, activated [activated recombinant human coagulation Factor VII (rFVIIa)] is structurally similar to human plasma-derived coagulation factor VIIa .This vitamin K-dependent glycoprotein is promoting hemostasis at the site of bleeding when the coagulation factors do not work correctly.

Eptacog alfa, activated is a replacement therapy that has changed the management of bleeding in patients with congenital disorders of coagulation, such as Hemophilia A/B with inhibitors, Congenital factor VII (FVII) deficiency and Glanzmann thromboasthenia.

Although therapeutic advances in control of bleeding episodes have led to a decreased morbidity and a better quality of life, the cost of treatment limits its access. This led to the development of a biosimilar version of of NovoSeven.

STUDY DESIGN

At Screening visit, visit 1, Patients will be assessed for inclusion and exclusion criteria and blood sampling for routine laboratory assessment of immunogenicity (antibody screening, pre-dose) will be obtained. This testing will be done at local laboratory. Screened patients will be enrolled if the results of antibodies assessed by the study local lab will be negative; samples will be stored and sent to the central lab (ERBC, Pomezia – Roma – Italy) later, for confirmation).

As soon as laboratory (local lab) results for immunogenicity will be available, patients will be scheduled for two dosing visits (visits 2 and 3) separated by a washout period of at least 3 days.

Patients will be hospitalized at time of study medication administration (AryoSeven or NovoSeven) and plasma sampling (visit 2-3). Before study medication administration plasma sample for immunogenicity will be obtained.

The assignment to a product or to the other will occur randomly (casually, by chance) accordingly to a randomization list generated by a computer.

At visit 2 and 3, patients will receive the study medication (both AryoSeven and NovoSeven, single dose injection separated by at least 3 days) and, after every dose of

drug, blood samples for laboratory testing of pharmacodynamics (PD), as TGA, D-dimer and F1-2, and pharmacokinetic (PK) will be collected from each patient.

For TGA and PK: 10 min prior to dose administration and at 10 min, 20 min, 1h, 3h, 5h, 8h and 12h; 24h and 30h post-dosing.
D-dimer and F1.2 will be tested on blood samples taken 10 min prior to dose administration and at 20 min, 1h, 5h, and 12h; 24h post-dosing.
The amount of blood that will be drawn during the blood sampling is 5 ml from the arm not used for rFVIIa infusion. For bioanalytical reasons, 9 ml of blood, instead of 5ml, will be drawn during the Visit 2 and Visit 3 at the timepoints1h and 12h.

At the end of this phase A, the patients will enter an open phase with the aim of monitoring of immunogenicity, clinical efficacy of safety data. Patients will be asked to:

1. return to the study center every time they have a bleeding, to receive treatment with AryoSeven for one of more days until resolution of bleeding, with dose and duration of treatment based on the Investigator's decision, for every bleeding episode that should occur during 12 months. Treatment with AryoSeven (study medication supplied by the study center) should be given at home, with dose and duration of treatment based on the Investigator's decision, and intravenous self-injection by the parent/caregiver/support person.

2. return to the center every 3 months for 1 year (4 visits) for blood sampling for immunogenicity study adverse event monitoring.

For every bleeding episode, the treatment response will be evaluated using a 4 point scale (Excellent, Good, Moderate, None), 2 h, 6 h and 12 h after drug infusion. Treatment should be assessed as failure if at least 3 doses of AryoSeven have been administered.

Patients should receive AryoSeven for prevention (prophylaxis) of bleeding, with dose and duration of treatment that will be based on the Investigator's decision

Plasma samples of all Patients will be periodically shipped from the study center to the central laboratory in Italy for analysis.

Assessment of biochemistry, hematology and coagulation-related parameters will be performed at screening (visit 1), pre-dosing at visit 2 and 3, and every 3 months in the follow up period of 12 months.

You will be asked to provide information on your primary disease and disease status, medical history, past and current concomitant diseases and treatments, demographic data, baseline characteristics: age, sex, baseline weight, height, race and surgical history, CNS function at study entry, physical examination findings.

You should contact the study doctor or site staff for any additional clarifications or if you experience any change in the way you feel following administration of the study drug.

Simultaneous use of prothrombin complex concentrates, activated or not , is NOT permitted.

Patients may NOT be treated concurrently with rFXIII medications.

Experience with concomitant administration of anti-fibrinolytics is limited and concomitant treatment with these products should be avoided.

POTENTIAL BENEFITS AND RISKS TO PARTICIPATE

The medicine (AryoSeven™) has shown similarity with the branded product (NovoSeven®) in all of previous laboratory and clinical researches. Also method of administration and dosage of this medicine are quite similar to branded product.

ARYOGEN biosimilar eptacog alfa (AryoSeven) has been studied in a multicenter randomized, controlled, double blind clinical trial with 66 patients with congenital factor VII deficiency (35 patients randomized to AryoSeven; 31 patients randomized to NovoSeven). There were no withdrawals due to adverse events, death, serious adverse events, or adverse events evaluated by the investigators as possibly or probably related to study medications. No serious adverse events have been observed during the study period (4 weeks) and the 3 months follow up. The numbers and types of adverse events were comparable with no significant difference between the two Arms.

However, this medicine like any other medicines may have side effects, all of patients are under full insurance coverage by AryoGen Pharmed Company for these possible side effects and all of treatment costs are covered by AryoGen Pharmed Co.

We cannot ensure that you will personally benefit from participating in this study. However, by taking part in this study you may contribute with new information that may benefit patients with hemophilia A/B with inhibitor in the future.

STUDY COST

Pharmaceutical products as well as diagnostic and therapeutic procedures are free for patients participating in the study and transportation costs will be compensated for them.

CONFIDENTIALITY

All data collected by this study will be used under legal standards. Data will be stored and processed anonymously i.e. your data will not be identified by the patient name but only by a patient number. This means that only anonymous data will be transmitted. Patient identity and anonymity will be treated as strictly confidential also in the case of a publication of the study results.

Representatives of the Sponsor or of the authorized Clinical Research Organization conducting the study and/or representatives of the responsible national health authorities will have the right to access medical data and to review study procedure without breaking of anonymity of study participants under the legal regulations. These inspections are performed for reasons of safety and reliability of the data. All persons involved are subject to a strict confidentiality agreement.

By signing this Informed Consent Form, your authorization and permission are given to the above mentioned representatives to access your medical records for the fulfillment of this study and for the processing of your personal data, as well as the transfer of such data outside your Country for the purposes of this clinical study, in accordance with the terms and mechanisms provided in this information sheet.

In accordance with the applicable local regulations and the General Data Protection Regulation (GDPR) n 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, the authorized Clinical Research Organization, Sintesi Research S.r.l., will treat your personal data exclusively to improve experimentation and for purposes of Pharmacovigilance. In carrying out this task the parties will not go beyond their respective competences and will comply with the requirements deriving from Good Clinical Practice. All personal information will remain confidential and it will be only used for statistical analysis by the research team.

STUDY PARTICIPATION

The Participation in this study is based completely on free will and you are free to withdraw your consent whenever you decide, without having to give a reason for doing so and without subjecting you to any disadvantages or prejudices.

If, after accepting initially to enter into the study, you decide you should not participate in the study any longer, you may withdraw your consent and your doctor will switch you to an alternative treatment among those available.

The decision to not participate in this study or to interrupt the participation at any time during the study will have no influence whatsoever on the quality of treatment you will get from your doctor.

The sponsor or your doctor may terminate your participation in the study if it is in the interest of your health to do so or should new information arise during the course of the study which could put your safety at risk.

INSURANCE

In case you should experience any damage caused by the study treatment you will receive adequate care and assistance without any expense for you.

This study is covered by Insurance Policy nr. _____stipulated by the Sponsor with the Insurance Company _____that will cover for any eventual damage to your health derived from study participation.

CONTACT INFORMATION

If you have any other additional questions concerning the study medication and protocol please contact your doctor _____ (name and surname) personally or by phone at the number _____ (telephone number).

Informed Consent Form for Adult Patients

Study title: A RANDOMIZED, MULTICENTER, DOUBLE BLIND CLINICAL TRIAL COMPARING PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY OF A BIOSIMILAR EPTACOG ALFA (AryoSeven) AND NOVOSEVEN®, IN PATIENTS WITH HAEMOPHILIA A OR B WITH INHIBITORS. UGA 2014-01.

I, _____

- I confirm that the study Doctor (Investigator) explained me the study, I read and understood this information sheet on (date) _____ and I had the opportunity to ask my questions.
- The study Doctor informed me of the risk and possible benefits associated with the participation in this study.
- I know that my participation in this study is voluntary and I can withdraw freely at any time without giving a reason and also my medical care or legal rights will not be affected.
- I authorize the study coordinator and his team involved in the study, the Sponsor of the study, the Medical Ethics Committee, the Office of Drug Supervision in MOH and any other Health Authority that need to inspect this study to observe my health records any time, during the study or later if any further investigation may be conducted related to this study (even if I withdraw from the study I agree with the access).
- However, I have been informed that my medical information will not be disclosed and such data will only be used for statistical purposes.
- I agree to participate in this study.
- I have received a signed copy of this Informed Consent for my information.

Name and signature of patient/legally representative:

_____

Patient's Name (Capital letters):

_____ _____

Patient's Signature Date

Investigator's Statement and Signature

I, the undersigned Dr. ..... , testify that Mr/Ms. ....., on reading the attached Information Sheet responded to all questions and signed his/her consent to participate in this Study, had clearly understood the information received and was capable of arriving at a fully informed choice.

I hereby declare that I have explained the above study and certify that to the best of my knowledge the subject signing this consent form understands the nature, demands, potential risks and benefits involved in participating in this study.

_____

Investigator's name (Capital letters)

_____ _____

Investigator's Signature Date

Note: one copy of this signed and dated Informed Consent form will be given to me for my records and future reference and original will be placed in the subject's file.

Information Sheet and Informed Consent Form for patient's parents

Study title: A RANDOMIZED, MULTICENTER, DOUBLE BLIND CLINICAL TRIAL COMPARING PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY OF A BIOSIMILAR EPTACOG ALFA (Aryoseven) AND NOVOSEVEN®, IN PATIENTS WITH HAEMOPHILIA A OR B WITH INHIBITORS.

Protocol Identifier: UGA 2014-01

Dear Parents,

We are inviting you to let your son to take part in a clinical trial, a type of research study, because your son has haemophilia A or B .
Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Take time to decide whether or not you wish to take part. You may discuss your possible participation in the study and alternative treatments with your family or any doctor.

The study doctor will give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

Maybe you do not understand some words. Please ask the study doctor to stop as you go through the information and the study doctor will take time to explain. If you have questions later, you can ask the study doctor or the staff.

AIM OF THE STUDY

This clinical trial is a comparative study between efficacy of recombinant activated factor VII produced by the Sponsor of the study, AryoGen Pharmed Company (AryoSeven™) and Novoseven®.

It is expected that at least 50 patients will take part in this research from various haemophilia centers in different Countries participating in this clinical trial.

We are doing this study to further complete the documentation on the product biosimilar eptacog alfa AryoSeven™. The aim of this study is to show that AryoSeven™ is similar to NovoSeven® .

INFORMATION ON THE TRIAL DRUG "AryoSeven™"

AryoGen biosimilar eptacog alfa (activated) is a biosimilar version of Novoseven® (Novo Nordisk) which is the Reference Medicinal Product (RMP).

The ARYOGEN biosimilar eptacog alfa is already marketed in Iran with the trade name AryoSeven.

The Company obtained advice from the European Medicine Agency (EMA) on 23 July 2015 and 15 September 2016 on questions concerning quality development, pre-clinical development and clinical development for obtaining Marketing Authorization in Europe.

Eptacog alfa, activated [activated recombinant human coagulation Factor VII (rFVIIa)] is structurally similar to human plasma-derived coagulation factor VIIa .This vitamin K-dependent glycoprotein is promoting hemostasis at the site of bleeding when the coagulation factors do not work correctly.

Eptacog alfa, activated is a replacement therapy that has changed the management of bleeding in patients with congenital disorders of coagulation, such as Hemophilia A/B with inhibitors, Congenital factor VII (FVII) deficiency and Glanzmann thromboasthenia.

Although therapeutic advances in control of bleeding episodes have led to a decreased morbidity and a better quality of life, the cost of treatment limits its access. This led to the development of a biosimilar version of of NovoSeven.

STUDY DESIGN

If disease and conditions of your child satisfy study inclusion criteria, you will be asked to sign the consent of study participation before any investigation is performed.

If you decide to let your son to participate and sign the Informed Consent form, your child will undergo to a full medical screening and to the following investigations.

At Screening visit, visit 1, your son will be assessed for inclusion and exclusion criteria and blood sampling for routine laboratory assessment of immunogenicity (presence of anti-Factor VII antibody screening) will be obtained. This testing will be done at local laboratory. Screened patients will be enrolled if the results of antibodies assessed by the study local lab will be negative (samples will be stored and sent to the central lab (RTC, Pomezia – Roma – Italy) later, for confirmation.

As soon as laboratory (local lab) results for immunogenicity will be available, your child will be scheduled for two dosing visits (visits 2 and 3) separated by a period of 3 days.

According to this type of study, he will be randomized (i.e, assigned by chance) to receive at visit 2 and 3 either a indistinguishable single therapeutic dose of NovoSeven® and one single dose of AryoSeven™, or vice versa, with doses at distance of three (3) days (this phase of the study is called “PK cross over and immunogenicity follow-up group”). Novoseven and AryoSeven are similar drugs.
Patients will be hospitalized at time of study medication administration and plasma sampling.

Your son will receive the product with undistinguishable syringes that is in double blinding (masking, by an independent operator). This means that the kind of medicine is kept masked from both the Doctors participating in this study and the Patient.

The assignment to a product or to the other will occur randomly (casually, by chance) accordingly to a randomization list generated by a computer.
At visit 2 and 3, your child will be hospitalized and blood sampling will be taken several time during the 24 hours: 10 min- prior to dose administration and at 10 min, 20 min, 1 h, 3 h, 5 h, 8 h, 12 h, 24 h and 30 h after AryoSeven or NovoSeven injection.
The amount of blood that will be drawn during the blood samples is 5 ml from the arm not used for rFVIIa infusion.

At the end of this phase, your son will be followed by the Doctors participating in this study for 12 months (this phase of the study is called “Immunogenicity Open follow up phase”), with periodic controls every 3 months for 1 year (4 visits) for blood sampling for determination of antibody formation (immunogenicity) monitoring.

During this period, your son will be treated with AryoSeven™ in Hospital, every time a bleeding should happen, with dose, frequency and duration of treatment that will be based on the Investigator’s decision, with the aim of monitoring inhibiting antibody formation, lack of efficacy and study adverse events. Treatment with AryoSeven should be given at home (study medication supplied by the study center), with dose and duration of treatment based on the Investigator’s decision, and intravenous self-injection by the parent/caregiver/support person.
Your son should receive AryoSeven for prevention (prophylaxis) of bleeding, with dose and duration of treatment that will be based on the Investigator’s decision

The modality of treatment with AryoSeven will be decided by the Investigator.

Blood sampling will be taken every 3 months.

Samples of all Patients will be periodically shipped from the study center laboratory to the central laboratory for confirmatory analysis.

Assessment of biochemistry, hematology, coagulation-related parameters and urine will be performed at screening (visit 1), pre-dosing at visit 2 and 3, and every 3 months in the follow up period of 12 months.

You will be asked to provide information on your child primary disease and disease status, medical history, past and current concomitant diseases and treatments, demographic data, baseline characteristics: age, sex, baseline weight, height, race and surgical history, CNS function at study entry, physical examination findings.

You should contact the study doctor or site staff for any additional clarifications or if you experience any change in the way your son/daughter feels following administration of the study drug.

Simultaneous use of prothrombin complex concentrates, activated or not – or – plasma, is NOT permitted.

Patients may NOT be treated concurrently with rFXIII medications.

Experience with concomitant administration of anti-fibrinolytics is limited and concomitant treatment with these products should be avoided.

POTENTIAL BENEFITS AND RISKS TO PARTICIPATE

The medicine (AryoSeven™) has shown similarity with the branded product (NovoSeven®) in all of previous laboratory and clinical researches. Also method of administration and dosage of this medicine are quite similar to branded product.

ARYOGEN biosimilar eptaco alfa (AryoSeven) has been studied in a multicenter randomized, controlled, double blind clinical trial with 66 patients with congenital factor VII deficiency (31 patients randomized to AryoSeven; 35 patients randomized to NovoSeven). There were no withdrawals due to adverse events, death, serious adverse events, or adverse events evaluated by the investigators as possibly or probably related to study medications. No serious adverse events have been observed during the study period and the 3 months follow up. The numbers and types of adverse events were comparable with no significant difference between the two Arms.

However, this medicine like any other medicines may have side effects, all of patients are under full insurance coverage by AryoGen Pharmed Company for these possible side effects and all of treatment costs are covered by AryoGen Pharmed Co.

The common Adverse Events observed in controlled and uncontrolled studies in patients that received AryoSeven or NovoSeven were: Headache, Nausea/Vomiting, Fever, Allergic, Leg pain, Chest pain, Arthralgia, Cyanosis, Pruritus, Dizziness, Hypoaesthesia, Rash, Infusion site rash, Urticaria and Hypotension.

We cannot ensure that your child will personally benefit from participating in this study. However, by taking part in this study you may contribute with new information that may benefit patients with Hemophillia A/B with inhibitor in the future.

STUDY COST

Pharmaceutical products as well as diagnostic and therapeutic procedures are free for patients participating in the study and transportation costs will be compensated for them.

CONFIDENTIALITY

All data collected by this study will be used under legal standards. Data will be stored and processed anonymously i.e. your child's data will not be identified by the patient name but only by a patient number. This means that only anonymous data will be transmitted. Patient identity and anonymity will be treated as strictly confidential also in the case of a publication of the study results.

Representatives of the Sponsor or of the authorized Clinical Research Organization conducting the study and/or representatives of the responsible national health authorities will have the right to access medical data and to review study procedure without breaking of anonymity of study participants under the legal regulations. These inspections are performed for reasons of safety and reliability of the data. All persons involved are subject to a strict confidentiality agreement.

By signing this Informed Consent Form, your authorization and permission are given to the above mentioned representatives to access your medical records for the fulfillment of this study and for the processing of your child personal data, as well as the transfer of such data outside your Country for the purposes of this clinical study, in accordance with the terms and mechanisms provided in this information sheet.

In accordance with the applicable local regulations and the General Data Protection Regulation (GDPR) n 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, the authorized Clinical Research Organization, Sintesi Research S.r.l., will treat your child personal data exclusively to improve experimentation and for purposes of Pharmacovigilance. In carrying out this task the parties will not go beyond their respective competences and will comply with the requirements deriving from Good Clinical Practice.

All personal information will remain confidential and it will be only used for statistical analysis by the research team.

STUDY PARTICIPATION

The Participation in this study is based completely on free will and you are free to withdraw your consent whenever you decide, without having to give a reason for doing so and without subjecting your child to any disadvantages or prejudices.

If, after accepting initially to enter into the study, you decide your child should not participate in the study any longer, you may withdraw your consent and your doctor will switch your child to an alternative treatment among those available.

The decision to not participate in this study or to interrupt the participation at any time during the study will have no influence whatsoever on the quality of treatment your child will get from your doctor.

The sponsor or your doctor may terminate the participation of your child in the study if it is in the interest of his/her health to do so or should new information arise during the course of the study which could put his/her safety at risk.

INSURANCE

In case your child should experience any damage caused by the study treatment, he/she will receive adequate care and assistance without any expense for you.

This study is covered by Insurance Policy nr. 5104/37/96/123 stipulated by the Sponsor with the Insurance Company Dana Insurance that will cover for any eventual damage to your child's health derived from study participation.

CONTACT INFORMATION

If you have any other additional questions concerning the study medication and protocol please contact your doctor _____ (name and surname) personally or by phone at the number _____ (telephone number).

Informed Consent Form for Patient's Parents

Study title: A RANDOMIZED, MULTICENTER, DOUBLE BLIND CLINICAL TRIAL COMPARING PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY OF A BIOSIMILAR EPTACOG ALFA (Aryoseven) AND NOVOSEVEN®, IN PATIENTS WITH HAEMOPHILIA A OR B WITH INHIBITORS. UGA 2014-01

We, the parents of, _____

- We confirm that the study Doctor (Investigator) explained us the study, We read and understood this information sheet on (date) _____ and we had the opportunity to ask our questions.
- The study Doctor informed us of the risk and possible benefits associated with the participation in this study.
- We know that the participation of our child in this study is voluntary and We can withdraw freely at any time without giving a reason and also his/her medical care or legal rights will not be affected.
- We authorize the study coordinator and his team involved in the study, the Sponsor of the study, the Medical Ethics Committee, the Office of Drug Supervision in MOH and any other Health Authority that need to inspect this study to observe my child's health records any time, during the study or later if any further investigation may be conducted related to this study (even if We withdraw from the study I agree with the access).
- However, We have been informed that the medical information of our son/daughter will not be disclosed and such data will only be used for statistical purposes.
- We agree to participate in this study.
- We have received a signed copy of this Informed Consent for my information.

_____

Mother / guardian Name (capital letters)

_____ _____

Mother / guardian Signature Date

_____

Father / guardian name (Capital letters)

_____ _____

Father / guardian Signature Date

Investigator's Statement and Signature

I, the undersigned Dr. ..... , testify that Mr/Ms. ....., on reading the attached Information Sheet responded to all questions and signed his/her consent to participate in this Study, had clearly understood the information received and was capable of arriving at a fully informed choice.

I hereby declare that I have explained the above study and certify that to the best of my knowledge the subject signing this consent form understands the nature, demands, potential risks and benefits involved in participating in this study.

_____

Investigator's name (Capital letters)

_____ ____ _____

Investigator's Signature Date

Note: one copy of this signed and dated Informed Consent form will be given to me for my records and future reference and original will be placed in the subject's file.

Information Sheet and Informed Consent Form for Adult Patients

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Protocol Identifier: UGA 2014-01

Dear Patient,

We are inviting you to take part in a clinical trial, a type of research study, because you have Hemophilia A/B with inhibitor titer.
Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Take time to decide whether or not you wish to take part. You may discuss your possible participation in the study and alternative treatments with your family or any doctor.

The study doctor will give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

Maybe you do not understand some words. Please ask the study doctor to stop as you go through the information and the study doctor will take time to explain. If you have questions later, you can ask the study doctor or the staff.

AIM OF THE STUDY

This clinical trial is a comparative study between efficacy of recombinant activated factor VII produced by the Sponsor of the study, AryoGen Pharmed Company (AryoSeven™) and NovoSeven®.

It is expected that at least 50 patients will take part in this research from various haemophilia centers in different Countries participating in this clinical trial.

We are doing this study to further complete the documentation on the product biosimilar eptacog alfa AryoSeven™. The aim of this study is to show that AryoSeven™ is similar to NovoSeven® .

INFORMATION ON THE TRIAL DRUG “AryoSeven™”

AryoGen biosimilar eptacog alfa (activated) is a biosimilar version of Novoseven® (Novo Nordisk) which is the Reference Medicinal Product (RMP).

The ARYOGEN biosimilar eptacog alfa is already marketed in Iran with the trade name AryoSeven.

The Company obtained advice from the European Medicine Agency (EMA) on 23 July 2015 and 15 September 2016 on questions concerning quality development, pre-clinical development and clinical development for obtaining Marketing Authorization in Europe.

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Eptacog alfa, activated is a replacement therapy that has changed the management of bleeding in patients with congenital disorders of coagulation, such as Hemophilia A/B with inhibitors, Congenital factor VII (FVII) deficiency and Glanzmann thromboasthenia.

Although therapeutic advances in control of bleeding episodes have led to a decreased morbidity and a better quality of life, the cost of treatment limits its access. This led to the development of a biosimilar version of of NovoSeven.

STUDY DESIGN

At Screening visit, visit 1, Patients will be assessed for inclusion and exclusion criteria and blood sampling for routine laboratory assessment of immunogenicity (antibody screening, pre-dose) will be obtained. This testing will be done at local laboratory. Screened patients will be enrolled if the results of antibodies assessed by the study local lab will be negative; samples will be stored and sent to the central lab (RTC, Pomezia – Roma – Italy) later, for confirmation).

As soon as laboratory (local lab) results for immunogenicity will be available, patients will be scheduled for two dosing visits (visits 2 and 3) separated by a washout period of 3 days.

Patients will be hospitalized at time of study medication administration (AryoSeven or Novoseven) and plasma sampling (visit 2-3). Before study medication administration plasma sample for immunogenicity will be obtained.

The assignment to a product or to the other will occur randomly (casually, by chance) accordingly to a randomization list generated by a computer.

At visit 2 and 3, patients will receive the study medication (both AryoSeven and Novoseven, single dose injection separated by at least 3 days) and, after every dose of drug, blood samples for laboratory testing of pharmacodynamics (PD), as TGA, D-dimer and F1-2, and pharmacokinetic (PK) will be collected from each patient.

For TGA and PK: 10 min prior to dose administration and at 10 min, 20 min, 1h, 3h, 5h, 8h and 12h; 24h and 30h post-dosing.

D-dimer and F1.2 will be tested on blood samples taken 10 min prior to dose administration and at 20 min, 1h, 5h, and 12h; 24h post-dosing.
The amount of blood that will be drawn during the blood sampling is 5 ml.

At the end of this phase A, patients will enter an open phase with the aim of monitoring of immunogenicity, clinical efficacy of safety data. Patients will be asked to:

1. return to the study center every time they have a bleeding, to receive treatment with AryoSeven for one of more days until resolution of bleeding, with dose and duration of treatment based on the Investigator's decision, for every bleeding episode that should occur during 12 months. Treatment with AryoSeven (study medication supplied by the study center) should be given at home, with dose and duration of treatment based on the Investigator's decision, and intravenous self-injection by the parent/caregiver/support person.

2. return to the center every 3 months for 1 year (4 visits) for blood sampling for immunogenicity study adverse event monitoring.

For every bleeding episode, the the treatment response will be evaluated using a 4 point scale (Excellent, Good, Moderate, None), 2 h, 6 h and 12 h after drug infusion. Treatment should be assessed as failure if at least 3 doses of AryoSeven have been administered.

Patients should receive AryoSeven for prevention (prophylaxis) of bleeding, with dose and duration of treatment that will be based on the Investigator's decision

Plasma samples of all Patients will be periodically shipped from the study center to the central laboratory in Italy for analysis.

Assessment of biochemistry, hematology, coagulation-related parameters and urine will be performed at screening (visit 1), pre-dosing at visit 2 and 3, and every 3 months in the follow up period of 12 months.

You will be asked to provide information on your primary disease and disease status, medical history, past and current concomitant diseases and treatments, demographic data, baseline characteristics: age, sex, baseline weight, height, race and surgical history, CNS function at study entry, physical examination findings.

You should contact the study doctor or site staff for any additional clarifications or if you experience any change in the way you feel following administration of the study drug.

Simultaneous use of prothrombin complex concentrates, activated or not , is NOT permitted.

Patients may NOT be treated concurrently with rFXIII medications.

Experience with concomitant administration of anti-fibrinolytics is limited and concomitant treatment with these products should be avoided.

POTENTIAL BENEFITS AND RISKS TO PARTICIPATE

The medicine (AryoSeven™) has shown similarity with the branded product (NovoSeven®) in all of previous laboratory and clinical researches. Also method of administration and dosage of this medicine are quite similar to branded product.

ARYOGEN biosimilar eptacog alfa (AryoSeven) has been studied in a multicenter randomized, controlled, double blind clinical trial with 66 patients with congenital factor VII deficiency (35 patients randomized to AryoSeven; 31 patients randomized to NovoSeven). There were no withdrawals due to adverse events, death, serious adverse events, or adverse events evaluated by the investigators as possibly or probably related to study medications. No serious adverse events have been observed during the study period (4 weeks) and the 3 months follow up. The numbers and types of adverse events were comparable with no significant difference between the two Arms.

However, this medicine like any other medicines may have side effects, all of patients are under full insurance coverage by AryoGen Pharmed Company for these possible side effects and all of treatment costs are covered by AryoGen Pharmed Co.

We cannot ensure that you will personally benefit from participating in this study. However, by taking part in this study you may contribute with new information that may benefit patients with Hemophillia A/B with inhibitor in the future.

STUDY COST

Pharmaceutical products as well as diagnostic and therapeutic procedures are free for patients participating in the study and transportation costs will be compensated for them.

CONFIDENTIALITY

All data collected by this study will be used under legal standards. Data will be stored and processed anonymously i.e. your data will not be identified by the patient name but only by a patient number. This means that only anonymous data will be transmitted. Patient identity and anonymity will be treated as strictly confidential also in the case of a publication of the study results.

Representatives of the Sponsor or of the authorized Clinical Research Organization conducting the study and/or representatives of the responsible national health authorities will have the right to access medical data and to review study procedure without breaking of anonymity of study participants under the legal regulations. These inspections are performed for reasons of safety and reliability of the data. All persons involved are subject to a strict confidentiality agreement.

By signing this Informed Consent Form, your authorization and permission are given to the above mentioned representatives to access your medical records for the fulfillment of this

study and for the processing of your personal data, as well as the transfer of such data outside your Country for the purposes of this clinical study, in accordance with the terms and mechanisms provided in this information sheet.

In accordance with the applicable local regulations and the General Data Protection Regulation (GDPR) n 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, the authorized Clinical Research Organization, Sintesi Research S.r.l., will treat your personal data exclusively to improve experimentation and for purposes of Pharmacovigilance. In carrying out this task the parties will not go beyond their respective competences and will comply with the requirements deriving from Good Clinical Practice.All personal information will remain confidential and it will be only used for statistical analysis by the research team.

STUDY PARTICIPATION

The Participation in this study is based completely on free will and you are free to withdraw your consent whenever you decide, without having to give a reason for doing so and without subjecting you to any disadvantages or prejudices.

If, after accepting initially to enter into the study, you decide you should not participate in the study any longer, you may withdraw your consent and your doctor will switch you to an alternative treatment among those available.

The decision to not participate in this study or to interrupt the participation at any time during the study will have no influence whatsoever on the quality of treatment you will get from your doctor.

The sponsor or your doctor may terminate your participation in the study if it is in the interest of your health to do so or should new information arise during the course of the study which could put your safety at risk.

INSURANCE

In case you should experience any damage caused by the study treatment,you will receive adequate care and assistance without any expense for you.

This study is covered by Insurance Policy nr. 5104/37/96/123 stipulated by the Sponsor with the Insurance Company Dana Insurance that will cover for any eventual damage to your health derived from study participation.

CONTACT INFORMATION

If you have any other additional questions concerning the study medication and protocol please contact your doctor _____ (name and surname)

personally or by phone at the number _____ (telephone number).

Informed Consent Form for Adult Patients

Study title: A RANDOMIZED, MULTICENTER, DOUBLE BLIND CLINICAL TRIAL COMPARING PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY OF A BIOSIMILAR EPTACOG ALFA (Aryoseven) AND NOVOSEVEN®, IN PATIENTS WITH HAEMOPHILIA A OR B WITH INHIBITORS. UGA 2014-01.

I, _____

- I confirm that the study Doctor (Investigator) explained me the study, I read and understood this information sheet on (date) _____ and I had the opportunity to ask my questions.
- The study Doctor informed me of the risk and possible benefits associated with the participation in this study.
- I know that my participation in this study is voluntary and I can withdraw freely at any time without giving a reason and also my medical care or legal rights will not be affected.
- I authorize the study coordinator and his team involved in the study, the Sponsor of the study, the Medical Ethics Committee, the Office of Drug Supervision in MOH and any other Health Authority that need to inspect this study to observe my health records any time, during the study or later if any further investigation may be conducted related to this study (even if I withdraw from the study I agree with the access).
- However, I have been informed that my medical information will not be disclosed and such data will only be used for statistical purposes.
- I agree to participate in this study.
- I have received a signed copy of this Informed Consent for my information.

Name and signature of patient/legally representative:

_____

Patient's Name (Capital letters):

_____ _____

Patient's Signature Date

Investigator's Statement and Signature

I, the undersigned Dr. ..... , testify that Mr/Ms. ....., on reading the attached Information Sheet responded to all questions and signed his/her consent to participate in this Study, had clearly understood the information received and was capable of arriving at a fully informed choice.

I hereby declare that I have explained the above study and certify that to the best of my knowledge the subject signing this consent form understands the nature, demands, potential risks and benefits involved in participating in this study.

_____

Investigator's name (Capital letters)

_____ _____

Investigator's Signature Date

Note: one copy of this signed and dated Informed Consent form will be given to me for my records and future reference and original will be placed in the subject's file.

Information Sheet and Informed Consent Form for patient's parents

Study title: A RANDOMIZED, MULTICENTER, DOUBLE BLIND CLINICAL TRIAL COMPARING PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY OF A BIOSIMILAR EPTACOG ALFA (Aryoseven) AND NOVOSEVEN®, IN PATIENTS WITH HAEMOPHILIA A OR B WITH INHIBITORS

Protocol Identifier: UGA 2014-01

Dear Parents,

We are inviting you to let your son to take part in a clinical trial, a type of research study, because your son has haemophilia A or B .
Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Take time to decide whether or not you wish to take part. You may discuss your possible participation in the study and alternative treatments with your family or any doctor.

The study doctor will give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

Maybe you do not understand some words. Please ask the study doctor to stop as you go through the information and the study doctor will take time to explain. If you have questions later, you can ask the study doctor or the staff.

AIM OF THE STUDY

This clinical trial is a comparative study between efficacy of recombinant activated factor VII produced by the Sponsor of the study, AryoGen Pharmed Company (AryoSeven™) and Novoseven®.

It is expected that at least 50 patients will take part in this research from various haemophilia centers in different Countries participating in this clinical trial.

We are doing this study to further complete the documentation on the product biosimilar eptacog alfa AryoSeven™. The aim of this study is to show that AryoSeven™ is similar to NovoSeven® .

INFORMATION ON THE TRIAL DRUG "AryoSeven™"

AryoGen biosimilar eptacog alfa (activated) is a biosimilar version of Novoseven® (Novo Nordisk) which is the Reference Medicinal Product (RMP).

The ARYOGEN biosimilar eptacog alfa is already marketed in Iran with the trade name

AryoSeven.

The Company obtained advice from the European Medicine Agency (EMA) on 23 July 2015 and 15 September 2016 on questions concerning quality development, pre-clinical development and clinical development for obtaining Marketing Authorization in Europe.

Eptacog alfa, activated [activated recombinant human coagulation Factor VII (rFVIIa)] is structurally similar to human plasma-derived coagulation factor VIIa .This vitamin K-dependent glycoprotein is promoting hemostasis at the site of bleeding when the coagulation factors do not work correctly.

Eptacog alfa, activated is a replacement therapy that has changed the management of bleeding in patients with congenital disorders of coagulation, such as Hemophilia A/B with inhibitors, Congenital factor VII (FVII) deficiency and Glanzmann thromboasthenia.

Although therapeutic advances in control of bleeding episodes have led to a decreased morbidity and a better quality of life, the cost of treatment limits its access. This led to the development of a biosimilar version of of NovoSeven.

STUDY DESIGN

If disease and conditions of your child satisfy study inclusion criteria, you will be asked to sign the consent of study participation before any investigation is performed.

If you decide to let your son to participate and sign the Informed Consent form, your child will undergo to a full medical screening and to the following investigations.

At Screening visit, visit 1, your son will be assessed for inclusion and exclusion criteria and blood sampling for routine laboratory assessment of immunogenicity (presence of anti-Factor VII antibody screening) will be obtained. This testing will be done at local laboratory. Screened patients will be enrolled if the results of antibodies assessed by the study local lab will be negative (samples will be stored and sent to the central lab later, for confirmation in Milan - Italy).

As soon as laboratory (local lab) results for immunogenicity will be available, your child will be scheduled for two dosing visits (visits 2 and 3) separated by a period of 2 weeks.

According to this type of study, he will be randomized (i.e, assigned by chance) to receive at visit 2 and 3 either a indistinguishable single therapeutic dose of NovoSeven® and one single dose of AryoSeven™, or vice versa, with doses at distance of two (2) weeks (this phase of the study is called “PK cross over and immunogenicity follow-up group”). Novoseven and AryoSeven are similar drugs.
Patients will be hospitalized at time of study medication administration and plasma sampling.

Your son will receive the product with undistinguishable syringes that is in double blinding (masking, by an independent operator). This means that the kind of medicine is kept masked from both the Doctors participating in this study and the Patient.

The assignment to a product or to the other will occur randomly (casually, by chance) accordingly to a randomization list generated by a computer.
At visit 2 and 3, your child will be hospitalized and blood sampling will be taken several time during the 24 hours: 10 min- prior to dose administration and at 10 min, 20 min, 1 h, 3 h, 5 h, 8 h, 12 h, 24 h and 30 h after AryoSeven or NovoSeven injection.
The amount of blood that will be drawn during the blood samples **is 5 ml** from the arm not used for rFVIIa infusion.

At the end of this phase, your son will be followed by the Doctors participating in this study for 12 months (this phase of the study is called “Immunogenicity Open follow up phase”), with periodic controls every 3 months for 1 year (4 visits) for blood sampling for determination of antibody formation (immunogenicity) monitoring. During this period, your son will be treated with AryoSeven™ in Hospital, every time a bleeding should happen, , with dose, frequency and duration of treatment that will be based on the Investigator’s decision, with the aim of monitoring inhibiting antibody formation, lack of efficacy and study adverse events. The modality of treatment with AryoSeven will be decided by the Investigator. Blood sampling will be taken every 3 months. If the first bleeding event happens before month 3, when immunogenicity testing is planned, blood sampling for immunogenicity study will be taken before treatment with AryoSeven is initiated.

Samples of all Patients will be periodically shipped from the study center laboratory to the central laboratory in Italy (Milan) for confirmatory analysis.

Assessment of biochemistry, hematology, coagulation-related parameters and urine will be performed at screening (visit 1), pre-dosing at visit 2 and 3, and every 3 months in the follow up period of 12 months.

You will be asked to provide information on your child primary disease and disease status, medical history, past and current concomitant diseases and treatments, demographic data, baseline characteristics: age, sex, baseline weight, height, race and surgical history, CNS function at study entry, physical examination findings.

You should contact the study doctor or site staff for any additional clarifications or if you experience any change in the way your son/daughter feels following administration of the study drug.

Simultaneous use of prothrombin complex concentrates, activated or not – or – plasma, is NOT permitted.

Patients may NOT be treated concurrently with rFXIII medications.

Experience with concomitant administration of anti-fibrinolytics is limited and concomitant treatment with these products should be avoided.

POTENTIAL BENEFITS AND RISKS TO PARTICIPATE

The medicine (AryoSeven™) has shown similarity with the branded product (NovoSeven®) in all of previous laboratory and clinical researches. Also method of administration and dosage of this medicine are quite similar to branded product.

ARYOGEN biosimilar eptaco alfa (AryoSeven) has been studied in a multicenter randomized, controlled, double blind clinical trial with 66 patients with congenital factor VII deficiency (31 patients randomized to AryoSeven; 35 patients randomized to NovoSeven). There were no withdrawals due to adverse events, death, serious adverse events, or adverse events evaluated by the investigators as possibly or probably related to study medications. No serious adverse events have been observed during the study period and the 3 months follow up. The numbers and types of adverse events were comparable with no significant difference between the two Arms.

However, this medicine like any other medicines may have side effects, all of patients are under full insurance coverage by AryoGen Pharmed Company for these possible side effects and all of treatment costs are covered by AryoGen Pharmed Co.

The common Adverse Events observed in controlled and uncontrolled studies in patients that received AryoSeven or NovoSeven were: Headache, Nausea/Vomiting, Fever, Allergic, Leg pain, Chest pain, Arthralgia, Cyanosis, Pruritus, Dizziness, Hypoaesthesia, Rash, Infusion site rash, Urticaria and Hypotension.

We cannot ensure that your child will personally benefit from participating in this study. However, by taking part in this study you may contribute with new information that may benefit patients with congenital factor VII deficiency in the future.

STUDY COST

Pharmaceutical products as well as diagnostic and therapeutic procedures are free for patients participating in the study and transportation costs will be compensated for them.

CONFIDENTIALITY

All data collected by this study will be used under legal standards. Data will be stored and processed anonymously i.e. your child's data will not be identified by the patient name but only by a patient number. This means that only anonymous data will be transmitted. Patient identity and anonymity will be treated as strictly confidential also in the case of a publication of the study results.

Representatives of the Sponsor or of the authorized Clinical Research Organization conducting the study and/or representatives of the responsible national health authorities will have the right to access medical data and to review study procedure without breaking

of anonymity of study participants under the legal regulations. These inspections are performed for reasons of safety and reliability of the data. All persons involved are subject to a strict confidentiality agreement.

By signing this form, your authorization and permission are given to the above-mentioned representatives to access the medical records of your child for the fulfillment of this study.

Clinart Representative
Tel: +97144370551
Add: Office # 101, Building # 26, Dubai Healthcare City, Dubai, UAE

Food and Drug Organization Representatives
Tel:+98(21) 6192 7000
Add: Fakhr Razi Street- Enghelab Avenue, Tehran, Iran

All personal information will remain confidential and it will be only used for statistical analysis by the research team.

STUDY PARTICIPATION

The Participation in this study is based completely on free will and you are free to withdraw your consent whenever you decide, without having to give a reason for doing so and without subjecting your child to any disadvantages or prejudices.

If, after accepting initially to enter into the study, you decide your child should not participate in the study any longer, you may withdraw your consent and your doctor will switch your child to an alternative treatment among those available.

The decision to not participate in this study or to interrupt the participation at any time during the study will have no influence whatsoever on the quality of treatment your child will get from your doctor.

The sponsor or your doctor may terminate the participation of your child in the study if it is in the interest of his/her health to do so or should new information arise during the course of the study which could put his/her safety at risk.

INSURANCE

In case your child should experience any damage caused by the study treatment, he/she will receive adequate care and assistance without any expense for you.

This study is covered by Insurance Policy nr. _____ stipulated by the Sponsor with the Insurance Company _____ that will cover for any eventual damage to your child's health derived from study participation.

CONTACT INFORMATION

If you have any other additional questions concerning the study medication and protocol please contact your doctor _____ (name and surname) personally or by phone at the number _____ (telephone number).

Informed Consent template Form for patient's Parents

Study title: A RANDOMIZED, MULTICENTER, DOUBLE BLIND CLINICAL TRIAL COMPARING PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY OF A BIOSIMILAR EPTACOG ALFA (Aryoseven) AND NOVOSEVEN®, IN PATIENTS WITH HAEMOPHILIA A OR B WITH INHIBITORS

We, the parents of, ……

- We confirm that the study Doctor (Investigator) explained us the study, We read and understood this information sheet on (date) …..... and We had the opportunity to ask our questions.
- The study Doctor informed us of the risk and possible benefits associated with the participation in this study.
- We know that the participation of our child in this study is voluntary and We can withdraw freely at any time without giving a reason and also his/her medical care or legal rights will not be affected.
- We authorize the study coordinator and his team involved in the study, the Sponsor of the study, the Medical Ethics Committee, the Office of Drug Supervision in MOH and any other Health Authority that need to inspect this study to observe my child's health records any time, during the study or later if any further investigation may be conducted related to this study (even if We withdraw from the study I agree with the access).
- However, We have been informed that the medical information of our son/daughter will not be disclosed and such data will only be used for statistical purposes.
- We agree to participate in this study.
- We have received a signed copy of this Informed Consent for my information.

_____

Mother / guardian Name (capital letters)

_____ _____

Mother / guardian Signature Date

_____

Father / guardian name (Capital letters)

_____ _____

Father / guardian Signature Date

Investigator's Statement and Signature

I, the undersigned Dr. ..... , testify that Mr/Ms. ....., on reading the attached Information Sheet responded to all questions and signed his/her consent to participate in this Study, had clearly understood the information received and was capable of arriving at a fully informed choice.

I hereby declare that I have explained the above study and certify that to the best of my knowledge the subject signing this consent form understands the nature, demands, potential risks and benefits involved in participating in this study.

_____

Investigator's name (Capital letters)

_____ ____ _____

Investigator's Signature Date

Note: one copy of this signed and dated Informed Consent form will be given to me for my records and future reference and original will be placed in the subject's file.

Information Sheet and Informed Consent Form for adult patients

Study title: A RANDOMIZED, MULTICENTER, DOUBLE BLIND CLINICAL TRIAL COMPARING PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY OF A BIOSIMILAR EPTACOG ALFA (AryoSeven™) AND NOVOSEVEN®, IN PATIENTS WITH HAEMOPHILIA A OR B WITH INHIBITORS

Protocol Identifier: UGA 2014-01

Dear Patient,

We are inviting you to take part in a clinical trial, a type of research study, because you have Hemophilia A/B with inhibitor titer. .
Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Take time to decide whether or not you wish to take part. You may discuss your possible participation in the study and alternative treatments with your family or any doctor.

The study doctor will give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

Maybe you do not understand some words. Please ask the study doctor to stop as you go through the information and the study doctor will take time to explain. If you have questions later, you can ask the study doctor or the staff.

AIM OF THE STUDY

This clinical trial is a comparative study between efficacy of recombinant activated factor VII produced by the Sponsor of the study, AryoGen Pharmed Company (AryoSeven™) and Novoseven®.

It is expected that at least 50 patients will take part in this research from various haemophilia centers in different Countries participating in this clinical trial.

We are doing this study to further complete the documentation on the product biosimilar eptacog alfa AryoSeven™. The aim of this study is to show that AryoSeven™ is similar to NovoSeven® .

INFORMATION ON THE TRIAL DRUG “AryoSeven™”

AryoGen biosimilar eptacog alfa (activated) is a biosimilar version of Novoseven® (Novo Nordisk) which is the Reference Medicinal Product (RMP).

The ARYOGEN biosimilar eptacog alfa is already marketed in Iran with the trade name

AryoSeven.

The Company obtained advice from the European Medicine Agency (EMA) on 23 July 2015 on questions concerning quality development, pre-clinical development and clinical development for obtaining Marketing Authorization in Europe.

Eptacog alfa, activated [activated recombinant human coagulation Factor VII (rFVIIa)] is structurally similar to human plasma-derived coagulation factor VIIa .This vitamin K-dependent glycoprotein is promoting hemostasis at the site of bleeding when the coagulation factors do not work correctly.

Eptacog alfa, activated is a replacement therapy that has changed the management of bleeding in patients with congenital disorders of coagulation, such as Hemophilia A/B with inhibitors, Congenital factor VII (FVII) deficiency and Glanzmann thromboasthenia.

Although therapeutic advances in control of bleeding episodes have led to a decreased morbidity and a better quality of life, the cost of treatment limits its access. This led to the development of a biosimilar version of NovoSeven.

STUDY DESIGN

At Screening visit, visit 1, Patients will be assessed for inclusion and exclusion criteria and blood sampling for routine laboratory assessment of immunogenicity (antibody screening, pre-dose) will be obtained. This testing will be done at local laboratory. Screened patients will be enrolled if the results of antibodies assessed by the study local lab will be negative (samples will be stored and sent to the central lab later, for confirmation in Milan - Italy).

As soon as laboratory (local lab) results for immunogenicity will be available, patients will be scheduled for two dosing visits (visits 2 and 3) separated by a washout period of 2 weeks.

Patients will be hospitalized at time of study medication administration (AryoSeven or Novoseven) and plasma sampling (visit 2-3). Before study medication administration plasma sample for immunogenicity will be obtained.

The assignment to a product or to the other will occur randomly (casually, by chance) accordingly to a randomization list generated by a computer.

At visit 2 and 3, patients will receive the study medication (AryoSeven or Novoseven single dose injection) and blood samples for PD and PK will be collected from each patient.

For TGA and PK: 10 mins prior to dose administration and at 10 min, 20 min, 1h, 3h, 5h, 8h and 12h; 24h and 30h post-dosing.
For D-dimer and F1.2: 10 mins prior to dose administration and at 20 min, 1h, 5h, and 12h; 24h post-dosing.
The amount of blood that will be drawn during the blood samples is **5 ml**.

At the end of this phase A, one month after the last dose, all patients will be tested for immunogenicity and if negative, patients will registered and will enter an open phase with

the aim of monitoring of immunogenicity, clinical efficacy of safety data. Patients will be instructed to:

1. return to the study center every time they have a bleeding, to receive treatment with AryoSeven for one of more days until resolution of bleeding, with dose and duration of treatment based on the Investigator's decision, for every bleeding episode that should occur during 12 months

2. return to the center every 3 months for 1 year (4 visits) for blood sampling for immunogenicity study adverse event monitoring.

For every bleeding episode, the Investigator will rate you the treatment response on a 4 point scale (Excellent, Good, Moderate, None), 2 h, 6 h and 12 h post infusion. Treatment should be assessed as failure if at least 3 doses of AryoSeven have been administered.

Samples of all Patients will be periodically shipped from the study center laboratory to the central laboratory in Italy (Milan) for confirmatory analysis.

Assessment of biochemistry, hematology, coagulation-related parameters and urine will be performed at screening (visit 1), pre-dosing at visit 2 and 3, and every 3 months in the follow up period of 12 months.

You will be asked to provide information on your primary disease and disease status, medical history, past and current concomitant diseases and treatments, demographic data, baseline characteristics: age, sex, baseline weight, height, race and surgical history, CNS function at study entry, physical examination findings.

You should contact the study doctor or site staff for any additional clarifications or if you experience any change in the way you feel following administration of the study drug.

Simultaneous use of prothrombin complex concentrates, activated or not, is NOT permitted.

Patients may NOT be treated concurrently with rFXIII medications.

Experience with concomitant administration of anti-fibrinolytics is limited and concomitant treatment with these products should be avoided.

POTENTIAL BENEFITS AND RISKS TO PARTICIPATE

The medicine (AryoSeven™) has shown similarity with the branded product (NovoSeven®) in all of previous laboratory and clinical researches. Also method of administration and dosage of this medicine are quite similar to branded product.

ARYOGEN biosimilar eptacog alfa (AryoSeven) has been studied in a multicenter randomized, controlled, double blind clinical trial with 66 patients with congenital factor VII deficiency (35 patients randomized to AryoSeven; 31 patients randomized to NovoSeven).

There were no withdrawals due to adverse events, death, serious adverse events, or adverse events evaluated by the investigators as possibly or probably related to study medications. No serious adverse events have been observed during the study period (4 weeks) and the 3 months follow up. The numbers and types of adverse events were comparable with no significant difference between the two Arms.

However, this medicine like any other medicines may have side effects, all of patients are under full insurance coverage by AryoGen Pharmed Company for these possible side effects and all of treatment costs are covered by AryoGen Pharmed Co.

We cannot ensure that you will personally benefit from participating in this study. However, by taking part in this study you may contribute with new information that may benefit patients with congenital factor VII deficiency in the future.

STUDY COST

Pharmaceutical products as well as diagnostic and therapeutic procedures are free for patients participating in the study and transportation costs will be compensated for them.

CONFIDENTIALITY

All data collected by this study will be used under legal standards. Data will be stored and processed anonymously i.e. your data will not be identified by the patient name but only by a patient number. This means that only anonymous data will be transmitted. Patient identity and anonymity will be treated as strictly confidential also in the case of a publication of the study results.

Representatives of the Sponsor or of the authorized Clinical Research Organization conducting the study and/or representatives of the responsible national health authorities will have the right to access medical data and to review study procedure without breaking of anonymity of study participants under the legal regulations. These inspections are performed for reasons of safety and reliability of the data. All persons involved are subject to a strict confidentiality agreement.

By signing this form, your authorization and permission are given to the above-mentioned representatives to access your medical records for the fulfillment of this study.

All personal information will remain confidential and it will be only used for statistical analysis by the research team.

STUDY PARTICIPATION

The Participation in this study is based completely on free will and you are free to withdraw your consent whenever you decide, without having to give a reason for doing so and without subjecting you to any disadvantages or prejudices.

If, after accepting initially to enter into the study, you decide you should not participate in the study any longer, you may withdraw your consent and your doctor will switch you to an alternative treatment among those available.

The decision to not participate in this study or to interrupt the participation at any time during the study will have no influence whatsoever on the quality of treatment you will get from your doctor.

The sponsor or your doctor may terminate your participation in the study if it is in the interest of your health to do so or should new information arise during the course of the study which could put your safety at risk.

INSURANCE

In case you should experience any damage caused by the study treatment, you will receive adequate care and assistance without any expense for you.

This study is covered by Insurance Policy nr. _____stipulated by the Sponsor with the Insurance Company _____that will cover for any eventual damage to your health derived from study participation.

CONTACT INFORMATION

If you have any other additional questions concerning the study medication and protocol please contact your doctor _____(name and surname) personally or by phone at the number _____(telephone number).

Informed Consent template Form for adult patients

Study title: A RANDOMIZED, MULTICENTER, DOUBLE BLIND CLINICAL TRIAL COMPARING PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY OF A BIOSIMILAR EPTACOG ALFA (AryoSeven™) AND NOVOSEVEN®, IN PATIENTS WITH HAEMOPHILIA A OR B WITH INHIBITORS

I, ……

- I confirm that the study Doctor (Investigator) explained me the study, I read and understood this information sheet on (date).....and I had the opportunity to ask my questions.
- The study Doctor informed me of the risk and possible benefits associated with the participation in this study.
- I know that my participation in this study is voluntary and I can withdraw freely at any time without giving a reason and also my medical care or legal rights will not be affected.
- I authorize the study coordinator and his team involved in the study, the Sponsor of the study, the Medical Ethics Committee, the Office of Drug Supervision in MOH and any other Health Authority that need to inspect this study to observe my health records any time, during the study or later if any further investigation may be conducted related to this study (even if I withdraw from the study I agree with the access).
- However, I have been informed that my medical information will not be disclosed and such data will only be used for statistical purposes.
- I agree to participate in this study.
- I have received a signed copy of this Informed Consent for my information.

Name and signature of patient/legally representative:

_____

Patient's Name (Capital letters)

_____ _____

Patient's Signature Date

Investigator's Statement and Signature

I, the undersigned Dr. ..... , testify that Mr/Ms. ....., on reading the attached Information Sheet responded to all questions and signed his/her consent to participate in this Study, had clearly understood the information received and was capable of arriving at a fully informed choice.

I hereby declare that I have explained the above study and certify that to the best of my knowledge the subject signing this consent form understands the nature, demands, potential risks and benefits involved in participating in this study.

_____

Investigator's name (Capital letters)

_____ _____

Investigator's Signature Date

Note: one copy of this signed and dated Informed Consent form will be given to me for my records and future reference and original will be placed in the subject's file.

MODULO DI INFORMAZIONE PER IL PAZIENTE

Titolo	Valutazione dell' efficacia e della tollerabilità di una soluzione per dialisi peritoneale contenente Glucosio, Xilitolo e L- Carnitina rispetto a soluzioni standard per dialisi peritoneale in Dialisi Peritoneale Ambulatoriale Continua (CAPD)
Sponsor	Iperboreal Pharma S.r.l.
Protocollo	IP-001-09
Eudract No	2009-016801-40
Versione	Finale 5.4 del 23 Aprile 2020

Gent.le Signora/Egr. Signore,
Le è stato chiesto di partecipare ad uno studio clinico e questo documento ha lo scopo di informarLa sulla natura dello studio. In questo stampato troverà dettagli sul tipo di sacche di soluzione dialitica che dovrà utilizzare, sul tipo di esami richiesti, le procedure e la durata della Sua partecipazione.

La prego di leggere attentamente queste informazioni scritte prima di prendere una decisione in merito ad una eventuale Sua partecipazione allo studio; Lei avrà a disposizione tutto il tempo necessario per decidere se partecipare o meno. Qualora dovesse trovare parole poco chiare o desiderasse maggiori informazioni, potrà porre liberamente qualsiasi domanda di chiarimento e riproporre ogni quesito che non abbia ricevuto una risposta chiara ed esauriente. Potrà inoltre rivolgersi alla Sua Famiglia o al Suo Medico prima di prendere qualsiasi decisione.

Nel caso in cui, dopo aver letto e compreso tutte le informazioni ivi fornite, decida di voler partecipare allo studio clinico, Le chiederò di voler firmare e personalmente datare il modulo di Consenso Informato allegato a questo documento.

CHE COSA SI PROPONE LO STUDIO
Come Lei sa, la dialisi peritoneale a cui è sottoposto serve a depurare il Suo organismo dalle sostanze tossiche che i Suoi reni, a causa della malattia da cui Lei è affetto, non riescono più ad eliminare adeguatamente. Il principio su cui si basa il processo di depurazione è quello di scambiare le sostanze tossiche a livello della membrana peritoneale. Durante la dialisi peritoneale una certa quantità di una soluzione per dialisi peritoneale viene inserita nel peritoneo attraverso un catetere Per questa ragione sono state studiate e prodotte sacche di soluzioni per dialisi peritoneale contenenti differenti composti osmoticamente attivi.
Tali liquidi inseriti nel peritoneo, vengono lasciati per un determinato tempo (4-6 ore) e successivamente recuperati con procedure di svuotamento del peritoneo che Le sono state insegnate.
Tali soluzioni di dialisi sono in grado di richiamare liquidi e sostanze tossiche del sangue mediante delle leggi fisiche di scambio attraverso il peritoneo basate su una maggiore concentrazione della soluzione di dialisi rispetto al sangue. Per ottenere tali concentrazioni a livello delle soluzioni di dialisi vengono aggiunte varie sostanze tra cui il glucosio ad alti dosaggi.
Il glucosio aggiunto alle soluzioni in quantità così elevate presenta però degli effetti indesiderati quali, ad esempio, ispessimento del peritoneo, riduzione della sua capacità di ultrafiltrazione, alterazione del metabolismo degli zuccheri e , in ultima analisi, la necessità di modificare la metodica dialitica (emodialisi).

Lo scopo di questo studio è di valutare la tollerabilità e l'efficacia dialitica di due soluzioni per dialisi peritoneale contenenti glucosio, Xilitolo e L- Carnitina verso soluzioni dialitiche standard per scambio notturno e scambi diurni..
Nello studio verranno inclusi 40 pazienti suddivisi in due gruppi di 20 pazienti ciascuno.
Il primo gruppo (GRUPPO A) riceverà una soluzione peritoneale per scambio notturno contenente glucosio (0,5%), Xilitolo (1,5%) e L- Carnitina (0,02%) verso una soluzione dialitica correntemente utilizzata contenente glucosio 2,5%.; il secondo gruppo (GRUPPO B) riceverà una soluzione peritoneale per scambio diurno contenente glucosio (0,5%), Xilitolo (0.7%) e L- Carnitina (0,02%) verso una soluzione dialitica correntemente utilizzata durante uno, due o tre scambi diurni contenente glucosio 1,5 %.

COSA COMPORTA LA SUA PARTECIPAZIONE ALLO STUDIO

Nel caso in cui Lei decidesse di partecipare allo studio, ci fornirà la possibilità di dimostrare l'efficacia dello Xilitolo e della L-Carnitina come agenti osmotici, aggiuntivi e non sostitutivi del glucosio, che dovrebbero portare ad una riduzione del carico quotidiano di glucosio a parità di efficacia depurativa e di determinare in modo accurato i quantitativi di carnitina assorbita dall'organismo per via intraperitoneale.

Lo studio avrà una durata complessiva di 12 settimane e comprenderà:

- un primo periodo di selezione (della durata massima di 28 giorni) durante il quale saranno valutate le Sue condizioni di base e la possibilità di poter essere incluso nella ricerca.
  All'inizio di questo periodo di osservazione Lei sarà assegnato ad uno dei due gruppi di trattamento e, in base al gruppo a cui sarà assegnato, utilizzerà per lo scambio notturno una soluzione contenente glucosio 2,5% (Gruppo A) oppure continuerà la Sua terapia standard (1, 2 o 3 scambi diurni più uno scambio notturno con icodestrina) (Gruppo B);
- un secondo periodo di trattamento, della durata di 4 settimane durante il quale sarà trattato con una soluzione per dialisi peritoneale contenente Glucosio (0.5%), Xilitolo (1.5%) and L-carnitine (0.02%) da utilizzare per lo scambio notturno (Gruppo A) o con una soluzione per dialisi peritoneale contenente Glucosio (0.5%), Xilitolo (0,7%) and L-carnitine (0.02%) da utilizzare per gli scambi diurni (1, 2 o 3 scambi) combinata con una soluzione di icodestrina per lo scambio notturno; (Gruppo B)
- Infine, un periodo di osservazione della durata anch'esso di 4 settimane in cui userà nuovamente la soluzione contenente glucosio al 2..5%. per lo scambio notturno (Gruppo A) oppure la Sua terapia standard (Gruppo B).

Durante tutta la durata della ricerca Lei potrà assumere tutti i farmaci ritenuti indispensabili per il trattamento di patologie concomitanti non correlate con quella in studio, purché non interferiscano con il trattamento oggetto della ricerca.

Se Lei è una donna in età fertile, potrà partecipare allo studio solo se avrà un test di gravidanza negativo prima dell'inizio del trattamento e se accetterà di evitare una gravidanza per tutta la durata dello studio prendendo adeguate misure anticoncezionali

Se accetterà di partecipare a questo studio Lei sarà sottoposta/o ad una prima accurata visita medica nel corso della quale il Medico Ricercatore verificherà se le Sue condizioni cliniche soddisfino i criteri richiesti dallo studio e saranno inoltre effettuate tutte le valutazioni cliniche e strumentali necessarie per l'esatta determinazione delle Sue condizioni basali.

Se al termine del periodo di selezione il Medico Ricercatore riterrà che Lei potrà essere inserito nello studio, Le verranno fornite le sacche contenenti Xilitolo e L-Carnitina per lo scambio notturno o per gli scambi diurni da utilizzare nei 28 giorni i successivi.

La informiamo, che la partecipazione alla ricerca non comporta per Lei alcun aggravio di spese.

La informiamo che, qualora Lei decida di partecipare allo studio il Medico Ricercatore provvederà ad informare il Suo Medico Curante in merito alla Sua partecipazione allo studio in modo che egli possa adeguare i suoi interventi allo studio stesso.

INDAGINI A CUI SARÀ SOTTOPOSTO/A DURANTE LO STUDIO

Se Lei accetterà di partecipare a questo studio, dopo aver letto e firmato questo modulo di consenso, sarà sottoposto/a alle seguenti indagini:

- ⇨ esame clinico generale durante il quale sarà effettuata un'attenta valutazione della Sua storia clinica, delle eventuali patologie concomitanti e dei trattamenti a cui Lei è stato sottoposto in precedenza e/o che continuerà nel corso dello studio;
- ⇨ esame fisico e rilevazione dei principali parametri clinici (peso, altezza, pressione arteriosa e frequenza cardiaca)
- ⇨ valutazione della diuresi ;
- ⇨ valutazione della funzionalità renale effettuata mediante alcuni prelievi ematici **(circa 10 ml)** ed urinari **(circa 10 ml.)** atti a determinare i parametri funzionali quali Kt/V, Clearance della creatinina, PET della creatinina e del glucosio e ultrafiltrazione ;
- ⇨ determinazione del CA125, che rappresenta un indice della sofferenza peritoneale, e il dosaggio delle proteine effettuati mediante un prelievo dal liquido di drenaggio della sacca dialitica al giorno -28, al giorno 0 e successivamente con periodicità bisettimanale;

- ⇨ valutazione elettrocardiografia effettuata al giorno 0, e alla fine del periodo di trattamento, giorno 28) consiste nel posizionare alcuni elettrodi sul Suo torace e valutare la funzionalità del cuore: è un test assolutamente non invasivo e non fastidioso; tale valutazione sarà effettuata all'inizio ed al termine dello studio;
- ⇨ valutazione delle concentrazioni del farmaco effettuata prelevando pochi millilitri di sangue **(circa 5 ml)** e raccogliendo circa 10 ml di urina e di liquido di drenaggio per determinare la concentrazione di L-Carnitina e dei suoi metaboliti. Tali determinazioni saranno effettuate anche prelevando liquido di drenaggio dalla sacca dialitica e sulle urine
- ⇨ determinazione dei principali parametri di laboratorio verrà effettuato prelevando un campione di sangue (circa 10ml) e raccogliendo un campione di urina.

Inoltre le verrà richiesto di compilare un Diario dove dovranno essere riportati le informazioni riguardanti il volume dell'ultrafiltrazione, il Suo peso, i farmaci assunti durante lo studio, l'eventuale comparsa di una manifestazione clinica indesiderata e il regolare uso delle sacche per dialisi peritoneale.

Lo studio prevede che effettuiate 6 controlli presso il Centro Sperimentale. Durante tali controlli saranno effettuati i seguenti esami.

Periodo di Selezione

Durante questo periodo saranno effettuati i seguenti esami e procedure.

- ⇨ Esame clinico e fisico completo (al giorno -28 e al giorno 0);
- ⇨ Valutazione della diuresi (al giorno -28 e al giorno 0);
- ⇨ Valutazione della funzionalità renale(al giorno -28 e al giorno 0);
- ⇨ Dosaggio del CA125 e della perdita di proteine nell'ultrafiltrato (al giorno -28 e al giorno 0);
- ⇨ Elettrocardiogramma (al giorno 0);
- ⇨ Test di gravidanza (al giorno -28)
- ⇨ Dosaggio della concentrazione delle Carnitine nel dialisato, nel sangue e nelle urine (al giorno 0);
- ⇨ Dosaggio dei principali parametri di laboratorio (al giorno -28 e al giorno 0);

Periodo di trattamento

I seguenti esami e procedure saranno effettuati nel corso di ogni singolo controllo

Giorno 14

- ⇨ Esame clinico e fisico completo
- ⇨ Valutazione della diuresi
- ⇨ Dosaggio del CA125 e della perdita di proteine nell'ultrafiltrato
- ⇨ Dosaggio delle Carnitine nel dialisato, nel sangue e nelle urine
- ⇨ Dosaggio dei principali parametri di laboratorio

Giorno 28

- ⇨ Esame clinico e fisico completo
- ⇨ Valutazione della diuresi
- ⇨ Valutazione della funzionalità renale
- ⇨ Dosaggio del CA125 e della perdita di proteine nell'ultrafiltrato
- ⇨ Elettrocardiogramma
- ⇨ Dosaggio delle Carnitine nel dialisato, nel sangue e nelle urine
- ⇨ Dosaggio dei principali parametri di laboratorio

Perodo di Follow-up

Giorno 42

- ⇨ Esame clinico e fisico completo
- ⇨ Valutazione della diuresi
- ⇨ Dosaggio delle Carnitine nel dialisato, nel sangue e nelle urine
- ⇨ Dosaggio dei principali parametri di laboratorio

Giorno 56

- ⇨ Esame clinico e fisico completo
- ⇨ Valutazione della diuresi
- ⇨ Valutazione della funzionalità renale

- ⇨ Dosaggio del CA125 e della perdita di proteine nell'ultrafiltrato
- ⇨ Dosaggio delle Carnitine nel dialisato, nel sangue e nelle urine
- ⇨ Dosaggio dei principali parametri di laboratorio

QUALI SONO I BENEFICI CHE POTRÀ RICEVERE PARTECIPANDO ALLO STUDIO

La Sua partecipazione sarà del tutto volontaria e qualora decidesse di ritirarsi non avrà alcuna conseguenza negativa sul Suo stato di salute. In qualsiasi momento dello studio Lei si potrà ritirare e non dovrà fornire alcuna spiegazione. In tal caso il Medico Ricercatore provvederà a darLe istruzioni su come riprendere il normale trattamento dialitico e Lei non subirà alcun danno dall'interruzione della terapia sperimentale.
La Sua partecipazione a questo studio non Le darà nessun beneficio diretto ed immediato, ma potrebbe ridurre l'insorgenza di patologie concomitanti quali diabete ed aumento di grassi nel sangue (iperlipidemie) usualmente causati dalla alta concentrazione di glucosio normalmente utilizzate nelle sacche per dialisi peritoneale in pazienti durante CAPD
Fino ad oggi la L-Carnitina è stata somministrata a migliaia di pazienti, essendo già commercializzata nella maggior parte dei Paesi della Comunità Europea e negli Stai Uniti per l'indicazione della deficienza primaria e secondaria di Carnitina e lo Xilitolo è molto usato in nutrizione parenterale in quei pazienti che non possono nutrirsi normalmente.

QUALI SONO I RISCHI DERIVANTI DALLA PARTECIPAZIONE ALLO STUDIO

La L-Carnitina è una sostanza naturalmente presente a livello dell'organismo ed è ben tollerata quando somministrata per via endovenosa o per via orale. La somministrazione per via intraperitoneale è stata testata in due precedenti esperienze su pazienti in trattamento con dialisi peritoneale ed è risultata anch'essa essere ben tollerata. E' registrata e venduta in Italia e in altri paesi per il trattamento delle deficienze primarie e secondarie di carnitina. Nelle deficienze secondarie di carnitina è inclusa anche l'insufficienza renale cronica terminale in trattamento emodialitico sostitutivo. Nei pazienti in dialisi viene somministrata alla dose di circa 2g alla fine di ogni seduta dialitica per via endovenosa.
L'aggiunta di L-Carnitina ad una sacca contenente la normale soluzione di dialisi non determina irritazione locale a livello del peritoneo. Non sono inoltre note interazioni della L-Carnitina con altri farmaci.
Lo Xilitolo è anch'esso presente a livello dell'organismo. Dal 1970 viene impiegato nei diabetici e nella nutrizione parenterale come sostitutivo del glucosio e successivamente è stato utilizzato in dialisi peritoneale. La somministrazione per via peritoneale è stata testata in una precedente esperienza a dosi maggiori di quelle proposte da questo studio, ed è risultata ben tollerata. Non sono note interazioni tra Xilitolo ed altri farmaci.

La informiamo che questo studio è coperto da una polizza assicurativa per la Responsabilità Civile verso Terzi, stipulata da Iperboreal Pharma s.r.l., con cui la compagnia assicuratrice si è obbligata a rispondere delle somme che la Contraente sia tenuta a pagare, quale civilmente responsabile ai sensi di legge, a titolo di risarcimento per ogni tipo di danno causato da prodotti medicinali, registrati o non, somministrati nel corso di sperimentazioni cliniche. Tale polizza non copre il valore eccedente il massimale di euro cinque milioni e tale copertura è operante esclusivamente per danni la cui richiesta di risarcimento sia stata presentata non oltre trentasei mesi dalla data di conclusione della sperimentazione. Tale limitazione non inficia il diritto del soggetto danneggiato ad ottenere il risarcimento da parte del responsabile. Inoltre la polizza assicurativa non risponde a risargimento per l'assunzione dei seguenti farmaci, assunti durante lo studio: anticocezionali ormonali, Stilbestrol/d.e.s.,Primidone, Fluoxetine, Phenylpropanolamine, Methylphenidate, Troglitazone, Gemifibrozil, Cerivastatin, Isotretinoin.

COSA SUCCEDE SE DECIDE DI NON PARTECIPARE ALLO STUDIO

Lei è libero/a di non partecipare allo studio oppure, se decide di partecipare, avrà il diritto di ritirarsi dallo studio in qualsiasi momento e senza l'obbligo di fornire spiegazioni. Anche il Medico Responsabile della ricerca potrà decidere di interrompere la partecipazione allo studio in qualsiasi momento lo ritenga opportuno, nel Suo interesse, senza che questo sia pregiudizievole per la Sua salute.
In caso insorga un problema medico conseguente la somministrazione del farmaco in studio Le saranno assicurate le cure più idonee in ambiente ospedaliero.

INTERRUZIONE DELLO STUDIO

La Sua adesione a questa ricerca è completamente volontaria e Lei si potrà ritirare dallo studio in qualsiasi momento.

Allo stesso modo, la sperimentazione potrà essere interrotta se il Medico constaterà che sono intervenuti effetti non desiderati.

In questo caso Lei sarà tempestivamente informato/a circa ulteriori trattamenti validi per la Sua malattia e potrà discuterne con il Medico.

INFORMAZIONI CIRCA I RISULTATI DELLO STUDIO

Se Lei lo richiederà, alla fine dello studio potranno esserLe comunicati i risultati dello studio in generale ed in particolare quelli che La riguardano.

ULTERIORI INFORMAZIONI

Lei potrà ottenere in qualsiasi momento ulteriori informazioni sullo studio clinico , sui Suoi diritti come partecipante allo studio e sui possibili rischi e se eventuali precauzioni chiamando Il Suo Medico Ricercatore.
Il Medico Ricercatore La informerà, inoltre,di qualsiasi innovazione nella terapia dialitica con xilitolo e carnitina che possa portarle beneficio o riduzione della sicurezza nelle procedure dello studio o qualsiasi informazione che possa influenzare la sua partecipazione a questo studio.

Per ulteriori informazioni e comunicazioni durante lo studio sarà a disposizione il seguente personale:

Dott./Prof. ....
Cognome nome

telefono .....

Il protocollo dello studio che Le è stato proposto è stato redatto in conformità alle Norme di Buona Pratica Clinica della Unione Europea ed in accordo ai principi etici espressi nelle Dichiarazione di Helsinki ed è stato approvato dal Comitato di Etica di questa struttura.
Lei potrà segnalare qualsiasi fatto ritenga opportuno evidenziare, relativamente alla ricerca che La riguarda, al Comitato di Etica e/o alla Direzione Sanitaria di questa struttura ospedaliera.

MODULO DI CONSENSO INFORMATO

Titolo	Valutazione dell' efficacia e della tollerabilità di una soluzione per dialisi peritoneale contenente Glucosio, Xilitolo e L- Carnitina rispetto a soluzioni standard per dialisi peritoneale in Dialisi Peritoneale Ambulatoriale Continua (CAPD)
Sponsor	Iperboreal Pharma S.r.l.
Protocollo	IP-001-09
Versione	Finale 5.4 del 23 Aprile 2020

Io sottoscritto ..... data di nascita ..... / ..... /.....
cognome e nome

Indirizzo .....
P.zza / Via / V.le

..... Numero Civico

Città ..... telefono .....

dichiaro di:

- partecipare volontariamente allo studio di cui mi sono stati spiegati, e di cui ho compreso lo scopo, le procedure alle quali potrò essere esposto, i possibili rischi e i benefici
- aver preso visione delle "Informazioni scritte per il Paziente" facenti parte di questo consenso, che confermano quanto mi è stato comunicato sullo studio e sul prodotto in sperimentazione
- aver avuto l'opportunità di porre domande chiarificatrici e di aver avuto risposte soddisfacenti
- aver avuto tutto il tempo necessario prima di decidere se partecipare o meno
- non aver avuto alcuna coercizione o influenza indebita nella richiesta del Consenso
- informare il Mio Medico Curante, in merito alla Mia partecipazione allo studio

Data ..... / ..... / ....
Firma del paziente

Io sottoscritto Prof./Dr. ....
Cognome Nome

- dichiaro che il paziente ha firmato spontaneamente la sua partecipazione allo studio
- dichiaro inoltre di:
  - aver fornito al paziente esaurienti spiegazioni in merito alle finalità dello studio, procedure, possibili rischi e benefici;
  - aver lasciato al Paziente il tempo necessario e la possibilità di fare domande in merito allo studio
  - non aver esercitato alcuna coercizione od influenza indebita nella richiesta del Consenso

Data ..... / ..... / ....
Firma del Medico che ha informato il Paziente
e richiesto il Consenso Informato

N.B.: una copia del presente modulo, firmato e datato, e delle "Informazioni Scritte per il Paziente" dovrà essere consegnata al Paziente stesso

Informativa e manifestazione del consenso al trattamento dei dati personali [1]

1. Titolari del trattamento e relative finalità

In conformità alla normativa locale applicabile (D.Lgs.190/2008 e D.Lgs.101/2018) ed al Regolamento Generale sulla Protezione dei Dati (GDPR) UE n. 2016/679 relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati , e alla normativa italiana di adeguamento, il Centro di sperimentazione_____, e l'Azienda farmaceutica *Iperboreal Pharma srl, Via Piave, 110/7 - 65122 Pescara (PE) - Italia*, che ha commissionato lo studio che Le è stato descritto, ciascuno per gli ambiti di propria competenza in qualità di autonomi titolari del trattamento ai sensi degli artt. 4,7 e 24 del Regolamento Generale sulla Protezione dei Dati (GDPR) UE n. 2016/679 e in accordo alle responsabilità previste dalle norme della buona pratica clinica (d.l. 211/2003), tratteranno i Suoi dati personali, in particolare quelli sulla salute e, soltanto nella misura in cui sono indispensabili in relazione all'obiettivo dello studio, altri dati relativi alla Sua origine, ai Suoi stili di vita e alla Sua vita sessuale, esclusivamente in funzione della realizzazione dello studio e a fini di farmacovigilanza. In aggiunta a tali finalità, i Suoi dati personali potranno essere trattati per la valutazione del prodotto oggetto dello studio da parte di potenziali acquirenti/licenziatari del prodotto. Nello svolgere tale compito le parti non andranno oltre le rispettive competenze e si conformeranno ai requisiti derivanti dalla Buona Pratica Clinica.

Lo scopo principale dello studio è la valutazione dell' efficacia e della tollerabilità di una soluzione per dialisi peritoneale contenente Glucosio Xilitolo e L- Carnitina rispetto a soluzioni standard per dialisi peritoneale in Dialisi Peritoneale Ambulatoriale Continua (CAPD).

A tali fini Suoi dati personali saranno raccolti dal Centro di sperimentazione e trasmessi all'Azienda farmaceutica e alle persone o società esterne che agiscono per loro conto, tra le quali la CRO delegata *Sintesi Research Srl, C.so di P.ta Romana, 132 – 20122 Milano (MI), Italia.*

È disponibile, su richiesta all'Azienda farmaceutica o alla CRO, l'elenco completo di eventuali terze parti, a cui potrebbero essere trasmessi i Suoi dati personali per i fini descritti in questo documento.

Il trattamento dei dati personali relativi alla Sua storia medica ed ai risultati delle analisi svolte sui campioni biologici da Lei prelevati è indispensabile allo svolgimento dello studio: il rifiuto di conferirli non Le consentirà di parteciparvi.

2. Natura dei dati

Il medico che La seguirà nello studio La identificherà con un codice: i dati che La riguardano raccolti nel corso dello studio, ad eccezione del Suo nominativo, saranno trasmessi all'Azienda farmaceutica, registrati, elaborati e conservati unitamente a tale codice, alla Sua data di nascita, al sesso, al Suo peso e alla Sua statura. Soltanto il medico e i soggetti autorizzati potranno collegare questo codice al Suo nominativo. Firmando questo consenso informato al trattamento dei dati personali, Lei autorizza e permette ai rappresentanti sopra citati ad accedere alle cartelle cliniche per l'adempimento degli obiettivi dello studio.

3. Modalità del trattamento dei dati e meccanismi di elaborazione

I dati che La riguardano e che verranno raccolti durante il corso dello studio, fatta eccezione per il Suo nome e cognome, saranno trattati in modo lecito, corretto e trasparente, in conformità alla

normativa locale applicabile (D.Lgs.190/2008 e D.Lgs.101/2018) ed al Regolamento Generale sulla Protezione dei Dati (GDPR) UE n. 2016/679 relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati.

Tali dati verranno trasmessi all'Azienda farmaceutica, memorizzati, elaborati e conservati in relazione al suddetto codice, alla Sua data di nascita, al Suo sesso, peso ed altezza (informazioni demografiche). I dati, trattati mediante strumenti anche elettronici, saranno diffusi solo in forma rigorosamente anonima, ad esempio attraverso pubblicazioni scientifiche, statistiche e convegni scientifici. La Sua partecipazione allo studio implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, il personale dell'Azienda farmaceutica o delle società esterne che eseguono per conto della prima il monitoraggio e la verifica dello studio, il Comitato Etico e le autorità sanitarie italiane e straniere potranno conoscere i dati che La riguardano, contenuti anche nella Sua documentazione clinica originale, con modalità tali da garantire la riservatezza della Sua identità.

4. Esercizio dei diritti

La informiamo che Lei potrà esercitare i diritti di cui all'art.15 e Sezioni 3 e 4 del Regolamento Generale sulla Protezione dei Dati (GDPR) UE n. 2016/679 (es. accedere ai Suoi dati personali, integrarli, aggiornarli, rettificarli, opporsi al loro trattamento per motivi legittimi, esercitare il diritto all'oblio e alla portabilità del dato, ecc.) rivolgendosi direttamente al Centro di sperimentazione, nella persona delegata al trattamento dei dati del centro di sperimentazione _____ oppure, alternativamente, contattando lo Sperimentatore Principale _____ oppure l'azienda farmaceutica promotrice dello studio *Iperboreal Pharma srl. (Dr. Arduino Arduini: a.arduini@iperboreal.com)* direttamente o tramite la persona di riferimento del centro sperimentale.

Le ricordiamo che potrà presentare un reclamo al Garante per la Protezione dei dati personali e che i suoi dati verranno conservati esclusivamente per il tempo necessario per conseguire le finalità per le quali sono stati raccolti e trattati.

5. Durata del trattamento dei dati

La durata dello studio per Lei é stimata essere da un minimo di 4 mesi circa fino a 7,5 mesi circa.

Le ricordiamo che la normativa sulle sperimentazioni cliniche di medicinali, che può essere applicata per analogia ad altre tipologie di studio, prevede che i documenti essenziali relativi allo studio debbano essere conservati presso l'Azienda farmaceutica e presso il Centro di sperimentazione per almeno sette anni dopo il completamento della sperimentazione, ovvero per un periodo di tempo più lungo in conformità alla disciplina applicabile o agli accordi intervenuti tra l'Azienda farmaceutica medesima ed il Centro di sperimentazione, ove esistenti (art. 18 D.Lgs. n. 200/2007; D.Lgs. n. 219/2006, all. 1, punto 5.2, lett. c); D.M. 15 luglio 1997, all. 1/4B, punti 4.9.4 e 4.9.5 e all. 1/5A, punti 5.5.11 e 5.5.12).

Ai sensi dell'art. 2 sexies del D.Lgs. 101/2018 la vigilanza sulle sperimentazioni riveste la qualifica di trattamento per motivi di interesse pubblico rilevante ai sensi dell'art. 9 paragrafo 2, lettera g) del Regolamento Generale sulla Protezione dei Dati (GDPR) UE n. 2016/679.

Le ricordiamo che Lei potrà interrompere in ogni momento e senza fornire alcuna giustificazione la Sua partecipazione allo studio: in tal caso, i campioni biologici a Lei correlati verranno distrutti. Non saranno inoltre raccolti ulteriori dati che La riguardano, ferma restando l'utilizzazione di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca.

6. Base giuridica del trattamento dei dati

Il Suo consenso costituisce la base giuridica del trattamento dei Suoi dati personali, ai sensi dell'art. 6, comma 1 lett. a) del Regolamento Generale sulla Protezione dei Dati (GDPR) UE n. 2016/679.

In merito al trattamento dei Suoi dati per la vigilanza sulle sperimentazioni, la base giuridica del trattamento è l'obbligo di legge cui è soggetto il titolare ai sensi dell'art. 6 parag. 1 lett c) del Regolamento Generale sulla Protezione dei Dati (GDPR) UE n. 2016/679.

7. Trasferimento dei dati verso Paesi extra-UE

Per quanto concerne l'eventuale trasferimento dei dati verso Paesi extra-UE, tra cui paesi che potrebbero non garantire il medesimo livello di tutela previsto dal Regolamento Generale sulla Protezione dei Dati (GDPR) UE n. 2016/679, il Centro di sperimentazione _____ e l'Azienda farmaceutica *Iperboreal Pharma srl, Via Piave, 110/7 - 65122 Pescara (PE) - Italia,* in qualità di autonomi titolari rendono noto che il trattamento avverrà comunque secondo una delle modalità consentite dal Regolamento Generale sulla Protezione dei Dati (GDPR) UE n. 2016/679, quali ad esempio il consenso dell'interessato, l'adozione di Clausole Standard approvate dalla Commissione Europea, la selezione di soggetti aderenti a programmi internazionali per la libera circolazione dei dati (es. EU-USA Privacy Shield) o operanti in Paesi considerati sicuri dalla Commissione Europea.

8. Consenso al trattamento dei dati

Preso atto dell'informativa di cui all'art. 13 del Regolamento Generale sulla Protezione dei Dati (GDPR) UE n. 2016/679, il/la sottoscritto/a:

□ **dà il proprio consenso** □ **nega il proprio consenso**

al trattamento dei dati personali per le finalità sopra descritte.

□ **dà il proprio consenso** □ **nega il proprio consenso**

al trasferimento dei dati personali in paesi terzi non appartenenti all'Unione Europea, nei limiti e con le modalità indicate nell'informativa fornita con il presente documento.

□ **dà il proprio consenso** □ **nega il proprio consenso**

alla eventuale cessione dei dati in forma anonima ad aziende farmaceutiche o ad altri soggetti che utilizzino gli stessi a scopo di studio o ricerca.

□ **dà il proprio consenso** □ **nega il proprio consenso**

affinché i risultati delle analisi e di eventuali scoperte inattese che emergano durante le attività di sperimentazione siano comunicate a:

□ me medesimo

□ familiare (Cognome e nome _____)

□ convivente / coniuge (Cognome e nome _____)

□ medico di famiglia (Cognome e nome _____)

Firma dell'interessato _____

Data _____

Nome e Cognome dell'interessato (in stampatello) _____

(1) Da sottoporre agli interessati unitamente al modulo di consenso informato che descrive le caratteristiche scientifiche dello studio, anche mediante integrazione dello stesso.
(2) Quando non è possibile conoscere al momento della redazione dell'informativa l'elenco completo dei soggetti terzi a cui i dati saranno trasmessi anche in paesi extra-UE occorre specificare come e quando l'elenco completo verrà reso disponibile.

16.1.4 LIST AND DESCRIPTION OF INVESTIGATORS AND DSMB

Principal Investigator	**Site #**	**Other Participants and their role in the Study**	
BONOMINI Mario Istituto di Clinica Nefrologica, , S.S. Annunziata Hospital / Università degli Studi G. D'Annunzio, Via dei Vestini Chieti, Italy	01	Lorenzo DI LIBERATO	Sub-investigator
		Carmela RAGO	Sub-investigator
		Teresa LOMBARDI	Sub-investigator
		Giorgia DI FULVIO	Sub-investigator
GESUALDO Loreto Dipartimento di Emergenza e Trapianti d'Organo, Sezione di Nefrologia, AO Universitario Consorziale, Policlinico di Bari Piazzale Giulio Cesare, 11 Bari, Italy	02	Roberto RUSSO	Sub-investigator
		Ilario RUSSO	Sub-investigator
		Giovanni PISCOPO	Sub-investigator
		Domenico ROSELLI	Site coordinator
		Cesira CAFIERO	Study nurse
		Luigi DE MAGGIS	Laboratory
		Saviana LO RUSSO	Laboratory
		Margherita PADOVAO	Pharmacist
GRANDALIANO Giuseppe Area Urologia-Nefrologia e Trapianti d'Organo, UOC Nefrologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Largo A. Gemelli, 8 Roma, Italy	03	Silvia D'ALONZO	Sub-investigator
		Maria Grazia PORRI	Sub-investigator
		Gianmarco DE LUCA	Sub-investigator
		Bettina BARTOLUCCI	Study nurse
		Valeria ALLEGRUCCI	Study nurse

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Informazioni personali

Nome(i) / Cognome	**Mario Bonomini**
Indirizzo del lavoro	58/A, Strada Vallone Fagnano, 66100, CHIETI, ITALIA
Telefono(i)	0871/358658 Cellulare:333/5959622
Fax	0871/574736
E-mail	mario.bonomini@unich.it
Nazionalità	Italiana
Codice fiscale	BNM MRA 61L16 A944R
Luogo e Data di nascita	Bologna 16/07/1961

Occupazione attuale e qualifica

Professore Ordinario di Nefrologia presso la Facoltà di Medicina e Chirurgia (attualmente Scuola di Medicina e Scienze della Salute) dell'Università degli Studi di Chieti dal 01/07/2021 alla data odierna

Esperienza professionale

Date	Ricercatore Universitario (settore scientifico-disciplinare F07F Nefrologia) presso l'Istituto di Clinica Nefrologica di Chieti dal 12.12.1988 al 12.12.1991 Ricercatore Universitario Confermato dal 12.12.1991 al 31.10.1998 Visiting Research Scientist nel 1991 e nel 1994 presso la Divisione di Nefrologia/Ipertensione del Dipartimento di Medicina della Northwestern University di Chicago, Illinois, USA Professore Associato di Nefrologia presso l'Università degli Studi di Chieti dal 1.11.1998 al 30.06.2021
Nome e indirizzo del datore di lavoro	"G. d'Annunzio" Università di Chieti-Pescara Via dei Vestini, 31 66100 Chieti
Tipo di azienda o settore	Università
Tipo di impiego	Professore Universitario/Primario Medico
Principali mansioni e responsabilità	Docente universitario/Dirigente Unità Complessa di Nefrologia Direttore Scuola di Specializzazione in Nefrologia

Istruzione e formazione

Date	1975-1980 Maturità Scientifica 1980-1986 Laurea in Medicina e Chirurgia con votazione di 110/110 e Lode presso l'Università degli Studi di Bologna 1987-1990 Specialista in Nefrologia presso l'Università "G. d'Annunzio" di Chieti-Pescara

Capacità e competenze personali

Madrelingua(e)	**Italiano**
Altra(e) lingua(e)	**Inglese**
Capacità di lettura	eccellente

Capacità di scrittura	eccellente
Capacità di espressione orale	eccellente

Capacità e competenze organizzative

Dirigente di 2° livello e Responsabile dell'Unità Operativa Complessa di Nefrologia e Dialisi presso l'Ospedale Clinicizzato "SS. Annunziata" di Chieti dal 1.1.1999

Direttore della Scuola di Specializzazione in Nefrologia della Scuola di Medicina e Scienza della Salute dell'Università "G. d'Annunzio" di Chieti-Pescara

Presidente della Sezione Interregionale A.La.M.M.U. (Abruzzo, Lazio, Marche, Molise, Umbria) della Società Italiana di Nefrologia per il biennio (2004-2006)

Capacità e competenze tecniche

Autore di 235 Pubblicazioni a Stampa comprendenti Capitoli in libri e Contributi Originali su argomenti di carattere nefrologico in italiano ed in inglese, oggetto di comunicazioni in occasione di molti Congressi nazionali ed internazionali

Interessi di ricerca:
Insufficienza renale cronica
Terapia sostitutiva artificiale dell'Uremia
Biocompatibilità
Farmacologia clinica
Elementi in tracce
Impiego della plasmaferesi
Progressione dell'insufficienza renale

Autorizzo il trattamento dei mei dati personali ai sensi del Decreto Legislativo 30 giugno 2003, n. 196 "Codice in masteria di protezione dei dati personali"

Data _Chieti, 16 febbraio 2022_____

Firma autografa

Curriculum Vitae

Surname: **Gesualdo** **Title**: MD, FERA
First Name: **Loreto**

Personal Data
Date of Birth: December 27th 1960
Place of Birth: Altamura (Italy) Nationality: Italian
Married, 3 sons

Career/Employment

Past

1987-1990	Research Associate, Institute of Pathology, CWRU, Cleveland, Ohio, USA
1994-2000	Staff physician, Institute of Nephrology, University of Bari
1997-1998	Visiting Professor, Department of Surgery, University of Pittsburgh
2000-2001	Associate Professor of Nephrology, University of Bari and Renal Division Chief, "Umberto I" Hospital, Altamura
2001-2003	Associate Professor of Nephrology, Chief of the Renal, Dialysis and Transplantation Unit, University Hospital of Foggia
2004-2007	Director of the Centre of Excellence "BIOAGROMED" for the application of Biotechnologies to Medicine and Food Quality
2003-2010	Full Professor of Nephrology, Chief of the Renal, Dialysis and Transplantation Unit, University Hospital of Foggia
2003-2010	Coordinator of the PhD Program "Molecular Medicine", School of Medicine, University of Foggia
2005-2010	Director of the Nephrology Resident Program, School of Medicine, University of Foggia
2006-2015	Chairman, Regional Competence Centers for Agri-Food Technologies (C.E.R.T.A)
2006-2010	Chairman, Apulian Regional Agri-Food Technology District (D.A.R.E.)
2007-2010	Director, Department of Nephrology, Dialysis and Tranplantation, Daunia Area (DIAN)
2007-2010	Council member, Italian Society of Nephrology
2009-2010	Member of the Evaluation Unit of the University of Foggia
2010-2015	Member, Steering Committee of Immunonephrology Working Group, ERA-EDTA
2012-2015	Council member, ERA-EDTA (European Society of Nephrology)
2012-2015	Member of the Group of Experts for Evaluation - 06 Area (GEV-06) of the ANVUR National Agency for Evaluation of the University and Research System
2010-2015	Director of the Nephrology Resident Program, School of Medicine, University of Bari
2016-2018	President, Italian Society of Nephrology
2010-pres	Full Professor of Nephrology, Chief of the Renal, Dialysis and Transplantation Unit, University Hospital "Policlinico" of Bari
2015-pres	Coordinator, Apulia Transplant Program
2015-pres	Chairman, CME Committee, European Society of Nephrology (ERA-EDTA)
2016-pres	Dean, School of Medicine, University of Bari
2018-pres	President Italian Kidney Foundation (FIR)
2020-pres	Member of Cultural scientific technical committee for the development of Strategic local plan "Taranto Futuro Prossimo"

Honors, Awards and Grants

Cum Laude Medical School Diploma, 1986; R.H. "Mike" Mohrman Research Fellowship, Kidney Foundation of Ohio, 1988-89; Italian Ministry of Public Education, Award 1988-1991; American Heart Association - Northeast Ohio Affiliate, Research Fellowship 1989-90; Kidney Foundation of Ohio, Research Grant 1989-90; "Young Investigator Scholarship" 22 July 1990, Tokyo, Japan; EDTA-ERA travel grant 1991, 1993, 1995; Gambro Fellowship, Lund, Sweden 1991-92; EDTA-ERA Junior Award 1992; CNR-NATO Fellowship 1997; NATO Collaborative Research grant; Baxter Extramural Grant, 1997-2000; Cassa di Risparmio di Puglia Foundation, Research Grant 2004-2005; Ministry of Health, Research Grant 2002-2015; PRIN MIUR, Research Grant 2002-2005; FIRB MIUR, Research Grant 2004-2008-2016; Remap (Erasmus+ KA grant: 2016-2018); Beat-DKD (IMI2, EU grant 2015-2020).

Membership: Italian Society of Nephrology; International Society of Nephrology; European Dialysis and Transplant Association; American Society of Nephrology; Renal Pathology Society.

Publications: Papers in PubMed more than 494 (Kidney International, New England Journal of Medicine, Journal of American Society of Nephrology, Journal Clinical Investigation, Journal of Immunology, Blood, Arterioscler Thromb Vasc Biol., Transplantation, Laboratory Investigation, Journal of Pathology, Journal of Experimental Medicine, American Journal of Kidney Diseases, Journal of Nephrology); number of communications to scientific meetings: more than 250; Books: 18. Total Impact Factor: more than 1500; Google Scholar: Total Citations: more than 20.000, H-score: 72. Scopus: Total Citations: more than 14.000, H-score: 50. RG Score: 50.50. I filed **four patents** and I have been honored with several awards.

Short report of my accomplishments

In this short report I would like to summarize my 30-year professional career from both the academic and medical point of view. Since 1987 I have dedicated myself with passion and tenacity to research, training and clinical practice. After spending three years at Case Western Reserve University, Cleveland, US, from 1987 to 1990, training in the field of renal immunopathology as a Research Associate, I returned to Italy where, at the University of Bari, I set up a research group that worked and produced scientific papers in the field of molecular biology applied to renal biopsy to elucidate the pathogenesis of renal fibrosis (1991-1996). This very fruitful period of my professional life has allowed me to be invited as a guest speaker to many national and international meetings. What is more, in this period I was able to put in place a team of highly motivated young researchers. As a visiting professor, in 1997-1998, I spent a training period at the University of Pittsburgh where I developed considerable expertise in the field of kidney cancer immunotherapy and renal transplant. Back to Italy, from 1999 to 2000 I continued my research work and clinical practice in Bari where I kept on training PhD and medical students. In 2001, I was appointed Chief of the Division of Nephrology, Dialysis and Transplantation Unit of the University of Foggia, Full Professor of Nephrology, and Coordinator of the "Molecular Medicine" PhD Program of the Medical School of the University of Foggia (2004-2010) and also Director of the Nephrology Resident Program of the Medical School of the University of Foggia, (2005-2010). The 10 years I spent in Foggia were very productive and saw me involved in many academic initiatives in my capacity as *Prorector* for Research and Chair of a Technological District. During the years in question I founded the "Bioagromed" Research Center where many young researchers, PhDs and medical students have received training in omics sciences. In 2010, I was back to the University of Bari, where I currently serve as the Chief of the Division of Nephrology, Dialysis and Transplantation Unit, as well as Coordinator of Regional Transplant Center (CRT) of Puglia and Dean of the Medical School of the University of Bari.

I served as a Member of the Steering Committee of the Immunonephrology Working Group, ERA-EDTA (2010-2015), and as a ERA-EDTA Council Member (2012-2015). I am currently President of Italian Society of Nephrology (2016-pres) and Chairman of ERA-EDTA Committee for CME activities.
Many of the PhD and medical students trained under my supervision have now become independent researchers. Over the last 30 years I have been either Coordinator or Principal Investigator of several international, national and regional project grants (NATO, PRIN , FIRB, Ministry of Health, AIFA and EU grants) collecting more than 20 million Euros. I have extensive research experience in renal disease, renal transplantation and renal cancer immunology in relation to inflammatory response, renal fibrosis, immunotherapy, regenerative medicine. My group has contributed to major developments in the field of renal fibrosis. In addition to clinical nephrology, my research efforts are also focused on experimental models of animal disease (IgA nephropathy). These studies allow us to explore the mechanisms underlying both development and course of glomerular and interstitial inflammation in renal disease. My recent research work aims to identify, by means of a "system biology" and a "Precision Medicine" approaches, biomarkers to be used to enhance diagnosis, prognosis and therapeutic outcomes in several chronic kidney diseases

(renal transplant, diabetic nephropathy, IgA nephropathy, Membranous GN, ADPKD, Rare Diseases in Nephrology).

I am a member of the Editorial Board of "Giornale Italiano di Nefrologia", "Journal of Nephrology", "Internal and Emergency Medicine", "Nephrology Dialysis and Transplantation", "Journal of Proteomics Insights".
I have served and still serve as a "peer reviewer" for the following journals: "Journal of the American Society of Nephrology"; "Kidney International"; "Proteomics"; "Journal of Immunology"; "American Journal of Kidney Diseases"; "Nephrology Dialysis and Transplantation"; "Nephron"; "Clinical Nephrology"; "Journal of Nephrology"; "Internal and Emergency Medicine", "PloS ONE"; "Giornale Italiano di Nefrologia".

I have several national and international collaborations in the United States, France and Germany. Finally, I have organized many international meetings, including the International Summer School of Renal Pathology (ISSRP), a two-week intensive program for practicing renal pathologists and nephrologists with an interest in improving their knowledge and clinical diagnostic skills.

WHAT OTHERS THINK OF LORETO GESUALDO

Opinion Leader in Nephrology. Excellent speaker, teacher and tutor. Excellent organizational and managerial skills, as well as an aptitude for coordinating team work. Excellent human qualities, from generosity to team spirit, contagious enthusiasm.

PARTICIPATION IN TV BROADCASTS

UNO Mattina, Mattino 5, Tutta Salute, Medicina 33, Storie Vere and many others local and regional TV.

HUMANITARIAN ACTIVITIES

Direct commitment to the establishment of a renal pathology center and a dialysis unit in Mbarara, Uganda.

ANVUR EVALUATION 2018-2020 (DM 8 Agosto 2018, N. 589) Scopus parameters (April 2020)

06/D2-MED/14	number of articles last 10 years	number of citations last 15 years	H index last 15 years
Threshold Full Professor	**44**	**1178**	**18**
Loreto Gesualdo	269	11366	53
Threshold Commissioner	**76**	**2319**	**25**
Loreto Gesualdo	269	11366	53

I consent to the management of my personal data according to decree 196/2003

Bari 12/02/2021

Prof. Loreto Gesualdo

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Informazioni personali

Nome / Cognome	**Giuseppe Grandaliano**
Indirizzo	Via A. Manzoni, 137, 70122, Bari, Italia
Telefono	3336960597
Fax	
E-mail	giuseppe.grandaliano@unicatt.it/giuseppe.grandaliano@policlinicogemelli.it
Cittadinanza	Italiana
Data di nascita	4 Settembre 1965
Sesso	Maschile

Esperienza professionale

1 Settembre 2019-Pres. Professore Ordinario di Nefrologia Università Cattolica del Sacro Cuore, Roma

1 Settembre 2019- Pres. Direttore, UOC Nefrologia, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Roma

25 Ottobre 2010-31 Agosto 2019 Direttore della Scuola di Specializzazione in Nefrologia dell'Università degli Studi di Foggia

25 Ottobre 2010-31 Agosto 2019 Direttore, UOC di Nefrologia, Dialisi e Trapianto, Azienda Ospedaliero-Universitaria "Ospedali Riuniti" di Foggia

25 Ottobre 2010-pres Professore Associato di Nefrologia dell'Università degli Studi di Foggia, Dipartimento di Scienze Mediche e Chirurgiche.

1 Novembre 2006-24 Ottobre 2010. Direttore della Scuola di Specializzazione in Nefrologia dell'Università degli Studi di Bari

1 Novembre 2002-24 Ottobre 2010. Professore Associato di Nefrologia dell'Università degli Studi di Bari presso il Dipartimento dell'Emergenza e dei Trapianti di Organo (DETO).

1 Novembre 2000-31 Ottobre 2002 Dirigente Medico di I livello presso l'U.O.C. di Nefrologia, Dialisi e Trapianto dell'Azienda Ospedaliera "Policlinico" di Bari.

3 Novembre 1998-31 Ottobre 2000 Dirigente Medico di I livello presso la U.O.C di Nefrologia e Dialisi del Presidio Ospedaliero di Barletta.

Gennaio-Settembre 1998 Dirigente Medico di I livello presso la U.O.C. di Nefrologia e Dialisi del Presidio Ospedaliero di Altamura.

Aprile-Giugno 1997 Dirigente Medico di I livello presso la U.O.C. di Nefrologia e Dialisi del Presidio Ospedaliero di Barletta.

Aprile 1994-Marzo 1997 Dirigente del servizio sanitario presso il Distretto Militare di Bari con il grado dapprima di sottotenente e quindi, dall'agosto 1996, di tenente.

Istruzione e formazione

1997 Research Fellowship, Div. of Nephrology, Dept of Medicine, University of Texas Health Science Center at San Antonio

1990-1994 Specializzazione in Nefrologia (50/50), Universita' degli Studi di Parma.

1991-1993 Research Fellowship, Div. of Nephrology, Dept of Medicine, University of Texas Health Science Center at San Antonio

1984-1990 Laurea in Medicina e Chirurgia (110/110 e lode), Università degli Studi di Ba (Laurea 9/7/1990).

1979-1984 Maturità Scientifica (60/60), Liceo Scientifico "A. Scacchi", Bari

Capacità e competenze personali

Madrelingua(e) **Italiano**

Altra(e) lingua(e)

Autovalutazione	Comprensione		Parlato		Scritto
Livello europeo (*)	Ascolto	Lettura	Interazione orale	Produzione orale	
Inglese	C2	C2	C2	C2	C2

Capacità e competenze sociali

Ha sempre svolto la propria attività clinica e di ricerca in equipe sviluppando capacità di gestione delle problematiche e delle conflittualità caratteristiche del lavoro di gruppo. Dal 2001 al 2008 ha svolto attività di Coordinamento nell'ambito del Centro Regionale Trapianti Puglia. Ha svolto funzione di tutor e supervisore nella formazione scientifica e clinica di numerosi studenti in Medicina e Chirurgia, dottorandi e specializzandi in Nefrologia. Ha partecipato all'organizzazione di numerosi Congressi Nazionali.

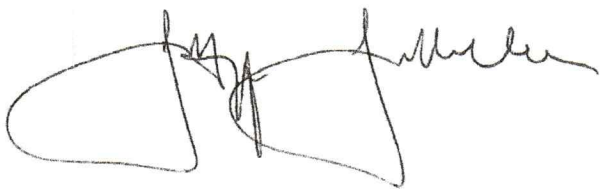
Dal 2011 al 2019 è stato parte del tavolo tecnico HTA di Nefrologia dell'Agenzia Regionale della Sanità (ARES) Puglia. Dal 2015 al 2018 è stato membro della Commissione Regionale trapianti e della Commissione Regionale Uremia.
E' membro del Rotary Club Bari Sud (Paul Harris Fellow).

Capacità e competenze organizzative	È Direttore della UOC di Nefrologia della Fondazione Policlinico Universitario "A. Gemelli" IRCCS con un reparto di degenza di 15 posti letto, due centri emodialitici con un totale di 45 posti tecnici in cui sono trattati 130 pazienti ed un centro di Dialisi Peritoneale con 70 pazienti. È stato Direttore dell'UOC di Nefrologia, Dialisi e Trapianto dell'Azienda Ospedaliero-Universitaria "Ospedali Riuniti" di Foggia con un reparto di degenza di 20 posti letto ed un centro emodialitico di 27 posti tecnici. Ha fatto parte del Direttivo di 3 gruppi di studio della Società Italiana di Nefrologia (Biologia Cellulare dal 1994 al 1996 e dal 2002 al 2004, Rene e Gravidanza dal 1996 al 1998 ed Immunopatologia renale dal 1997 al 1999). Dal 2012 al 2014 ha fatto parte del Direttivo della Società Italiana dei Trapianti di Organo (SITO) e nel periodo 2013-2014 ha ricoperto il ruolo di Segretario. Dal 2016 al 2019 è stato membro del direttivo dell'Immunonephrology Working Group della ERA-EDTA. Dal Dal 1 gennaio 2017 è membro del Consiglio di Amministrazione della Fondazione Italiana per la Promozione dei Trapianti di Organo (FIPTO). Dal 1 ottobre 2019 è il Coordinatore del Collegio Inter-societario SIN-SITO per il trapianto di rene. Dal 15 gennaio 2021 è membro della Commissione Scientifica del Centro Nazionale Trapianti. Dal 4 Dicembre 2021 è membro del Comitato Tecnico-Scientifico della SIN. Ha coordinato tre progetti di rilevante interesse nazionale (PRIN) finanziati dal Ministero dell'Università e della Ricerca Scientifica (2003-2005, 2005-2007 e 2010-2012). E' stato coordinatore nazionale di due progetti triennali (2007-2009) di Ricerca Finalizzata finanziati. È stato Direttore della Scuola di Specializzazione in Nefrologia dell'Università di Bari dal 2006 al 2010 e della Scuola di Specializzazione di Foggia dal 2010 al 2019. E' Direttore della Scuola di Specializzazione in Nefrologia dell'Università Cattolica del Sacro Cuore a partire dal 1 Novembre 2019.
Ulteriori informazioni	È autore di 223 pubblicazioni su riviste internazionali recensite da Pubmed (Impact factor medio dei 197 contributi originali sottoposti a peer review system 5,202), 7749 citazioni, h-index di 43 (Scopus). È membro dell'Editorial Board di 2 riviste nazionali (Giornale Italiano di Nefrologia e Minerva Nefrologica e Urologica) e quattro riviste internazionali (BMC Nephrology, Journal of Nephrology, Clinical Kidney Journal, World Journal of Transplantation). Referee di 12 riviste internazionali.

Autorizzo il trattamento dei dati personali contenuti nel mio curriculum vitae in base all'art.13 del D.Lgs. 196/2003 e all'art.13 del Regolamento UE 2016/679 (GDPR) ai fini stessi dell'accreditamento ECM e di tutte le procedure ad esso riconducibili]

Roma 21 Gennaio 2022

Firma



16.1.5 SIGNATURE(S) OF PRINCIPAL OR COORDINATING INVESTIGATOR(S) OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

16.1.5.1 Signature of Sponsor's Responsible Medical Officer

STUDY TITLE: Efficacy and safety assessments of a peritoneal dialysis solution containing Glucose, Xylitol and L-Carnitine compared to standard PD solutions in Continuous Ambulatory Peritoneal Dialysis (CAPD).

SPONSOR 'S RESPONSIBLE MEDICAL OFFICER:

NAME:	Arduino Arduini, M.D.
TITLE	Sponsor's Responsible Medical Officer
AFFILIATION:	Iperboreal Pharma

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

SIGNATURE	
DATE	08/02/2024

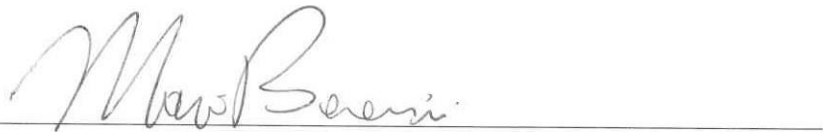
16.1.5.2 Signature of Principal Investigator

STUDY TITLE: Efficacy and safety assessments of a peritoneal dialysis solution containing Glucose, Xylitol and L-Carnitine compared to standard PD solutions in Continuous Ambulatory Peritoneal Dialysis (CAPD)..

PRINCIPAL INVESTOGATOR:

NAME:	Bonomini Mario, M.D.
TITLE	Director Nephrology
AFFILIATION:	SS Annunziata Hospital — Universitå degli Studi G. D'Annunzio, Chieti, Italy

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE 

DATE 08/02/2024

16.1.6 LISTING OF SUBJECTS RECEIVING TEST DRUGS/INVESTIGATIONAL PRODUCTS FROM SPECIFIC BATCHES

The following batch numbers were used in the Study Protocol IP-001-09:

Batch Numbers	
IPX15	9501053-a
IPX07	2100460
	1902

NovoSeven Batch Numbers	
PK/PD Phase	FS60V42
	FS60V43
	GS62T92
	GS63Y54
	JS69C21
	KS6AJ96
	JS69V60

16.1.7 RANDOMIZATION SCHEME AND CODES

This study was not randomised.

16.1.8 AUDIT CERTIFICATES

Not applicable

16.1.9 DOCUMENTATION OF STATISTICAL METHODS (DATA MANAGEMENT PLAN, STATISTICAL ANALYSIS PLAN; STATISTICAL OUTPUT)

16.1.9.1 Statistical Analysis Report

Study **IP-001-09**

Efficacy and safety assessments of a peritoneal dialysis solution containing Glucose, Xylitol and L-Carnitine compared to standard PD solutions in Continuous Ambulatory Peritoneal Dialysis (CAPD)

Statistical analysis – Report

Date: 07/09/2023

Version: final

Author: Antonio Colantoni

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Table 1 : Disposition of patients

	Group A* No. pts (%)	Group B* No. pts (%)	All No. pts (%)
Screened patients			15
Inclusion/Exclusion criteria not fulfilled			2**
All Inclusion/Exclusion criteria fulfilled	7(100.0%)	6(100.0%)	13 (86.7%)
Enrolled patients	7	6	13
Study completed according to the protocol	6 (85.7%)	6(100.0%)	12 (92.3%)
Patient with a complete treatment	6 (85.7%)	6(100.0%)	12 (92.3%)
Principal Reason for Subject Premature discontinuation			
Lost to follow up	1		1

*) Group A: experimental solution IPX15 for the nocturnal exchange
Group B: experimental solution IPX07 for the diurnal exchanges, combined with icodextrin for the nocturnal dwell

**) Reason for exclusion: patient has been treated with 2.5% glucose solution bags before Day 0 Visit

Table 2.1 : Demography and Medical history - Screened patients

	All No. pts (%)
Screened patients	15
Sex	
Male	12 (80.0%)
Female	3 (20.0%)
Age (years)	
no. pts.	15
Mean	68.47
SD	11.80
Median	70.00
Min : Max	37.00 : 86.00
Race	
White	15(100.0%)
Hospitalized/Outpatient patient	
Outpatient patient	15(100.0%)
Any significant medical or surgery history?	
Yes	15(100.0%)
Any treatment in the last 3 months?	
Yes	15(100.0%)
Any clinically significant abnormality?	
Yes	1 (6.6%)
No	14 (93.3%)

Table 2.2 : Demography and Medical history - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Enrolled patients	7	6	13
Sex			
Male	4 (57.1%)	6(100.0%)	10 (76.9%)
Female	3 (42.9%)		3 (23.1%)
Age (years)			
no. pts.	7	6	13
Mean	69.14	63.67	66.62
SD	5.01	16.17	11.38
Median	70.00	62.50	67.00
Min : Max	60.00 : 75.00	37.00 : 82.00	37.00 : 82.00
Race			
White	7(100.0%)	6(100.0%)	13(100.0%)
Hospitalized/Outpatient patient			
Outpatient patient	7(100.0%)	6(100.0%)	13(100.0%)
Any significant medical or surgery history?			
Yes	7(100.0%)	6(100.0%)	13(100.0%)
Any treatment in the last 3 months?			
Yes	7(100.0%)	6(100.0%)	13(100.0%)
Any clinically significant abnormality?			
Yes		1 (16.7%)	1 (7.7%)
No	7(100.0%)	5 (83.3%)	12 (92.3%)

Table 2.3 : Physical examination – abnormalities - Enrolled patients

Treatment group	Patient no.	Visit	abnormality
Group B	01-001	Screening Period: Day -28	RIGHT LOWER LIMB EDEMA

Note: no other abnormality was evidenced during the study

Table 3.1 : Clinical parameters - Screening visit - Screened patients

	All No. pts (%)
Height (cm)	
no. pts.	15
Mean	169.27
SD	7.58
Median	169.00
Min : Max	155.00 : 186.00
Weight (kg)	
no. pts.	15
Mean	78.86
SD	14.27
Median	80.00
Min : Max	51.00 : 100.00
Systolic Blood Pressure (mmHg)	
no. pts.	15
Mean	145.00
SD	12.39
Median	145.00
Min : Max	125.00 : 170.00
Diastolic Blood Pressure (mmHg)	
no. pts.	15
Mean	81.53
SD	8.84
Median	80.00
Min : Max	70.00 : 100.00
Heart Rate (beats/min)	
no. pts.	15
Mean	68.13
SD	10.76
Median	68.00
Min : Max	55.00 : 100.00
Diuresis (L/day)	
no. pts.	15
Mean	1.69
SD	0.51
Median	2.00
Min : Max	0.50 : 2.50
Does the patient show hyperhydratation signs?	
No	15(100.0%)

_____

Table 3.2 : Clinical parameters - Screening visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Height (cm)			
no. pts.	7	6	13
Mean	166.71	172.83	169.54
SD	7.23	8.52	8.15
Median	165.00	173.50	170.00
Min : Max	155.00 : 175.00	160.00 : 186.00	155.00 : 186.00
Weight (kg)			
no. pts.	7	6	13
Mean	78.71	81.45	79.98
SD	16.85	14.02	15.03
Median	80.00	84.00	82.00
Min : Max	51.00 : 98.00	64.20 : 100.00	51.00 : 100.00
Systolic Blood Pressure (mmHg)			
no. pts.	7	6	13
Mean	149.29	143.33	146.54
SD	14.27	8.76	11.97
Median	150.00	142.50	150.00
Min : Max	125.00 : 170.00	130.00 : 155.00	125.00 : 170.00
Diastolic Blood Pressure (mmHg)			
no. pts.	7	6	13
Mean	78.57	87.50	82.69
SD	6.90	8.80	8.81
Median	80.00	85.00	80.00
Min : Max	70.00 : 90.00	80.00 : 100.00	70.00 : 100.00
Heart Rate (beats/min)			
no. pts.	7	6	13
Mean	63.57	75.17	68.92
SD	7.09	12.58	11.28
Median	63.00	70.50	69.00
Min : Max	55.00 : 74.00	65.00 : 100.00	55.00 : 100.00
Diuresis (L/day)			
no. pts.	7	6	13
Mean	1.89	1.57	1.74
SD	0.20	0.74	0.53
Median	2.00	1.70	2.00
Min : Max	1.50 : 2.00	0.50 : 2.50	0.50 : 2.50
Does the patient show hyperhydratation signs?			
No	7(100.0%)	6(100.0%)	13(100.0%)

Table 4.1.1 : Ultrafiltration (Daily/Nocturnal Bag and Total) - Screening visit - Screened patients

	All No. pts (%)
1st Daily Bag (mL)	
no. pts.	15
Mean	226.67
SD	416.99
Median	100.00
Min : Max	-100.0 : 1500.0
2nd Daily Bag (mL)	
no. pts.	15
Mean	100.00
SD	391.43
Median	0.00
Min : Max	-150.0 : 1500.0
3rd Daily Bag (mL)	
no. pts.	15
Mean	16.67
SD	64.55
Median	0.00
Min : Max	0.00 : 250.00
Nocturnal Bag (mL)	
no. pts.	15
Mean	180.00
SD	426.70
Median	0.00
Min : Max	-150.0 : 1500.0
Total ultrafiltration (mL)	
no. pts.	15
Mean	523.33
SD	1122.0
Median	200.00
Min : Max	-100.0 : 4500.0

Table 4.1.2 : Ultrafiltration (CA 125S, Proteins) and Uric acid - Screening visit - Screened patients

	All No. pts (%)
CA 125 (U.a./mL)	
no. pts.	14
Mean	42.36
SD	26.12
Median	35.85
Min : Max	8.10 : 106.30
Proteins in ultrafiltration (mg/L)	
no. pts.	14
Mean	4.53
SD	6.57
Median	2.20
Min : Max	0.80 : 20.00
Uric acid (mg/dL)	
no. pts.	15
Mean	4.75
SD	1.70
Median	4.50
Min : Max	1.90 : 8.90
Uric acid - Evaluation	
Normal	10 (66.6%)
Not Clinically Significant	5 (33.3%)

Table 4.2.1 : Ultrafiltration (Daily/Nocturnal Bag and Total) - Screening visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
1st Daily Bag (mL)			
no. pts.	7	6	13
Mean	142.86	400.00	261.54
SD	190.24	614.00	439.30
Median	100.00	100.00	100.00
Min : Max	-100.0 : 500.00	-100.0 : 1500.0	-100.0 : 1500.0
2nd Daily Bag (mL)			
no. pts.	7	6	13
Mean	0.00	250.00	115.38
SD	0.00	619.68	420.51
Median	0.00	50.00	0.00
Min : Max	0.00 : 0.00	-150.0 : 1500.0	-150.0 : 1500.0
3rd Daily Bag (mL)			
no. pts.	7	6	13
Mean	0.00	41.67	19.23
SD	0.00	102.06	69.34
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	0.00 : 250.00	0.00 : 250.00
Nocturnal Bag (mL)			
no. pts.	7	6	13
Mean	0.00	450.00	207.69
SD	0.00	603.32	454.08
Median	0.00	300.00	0.00
Min : Max	0.00 : 0.00	-150.0 : 1500.0	-150.0 : 1500.0
Total ultrafiltration (mL)			
no. pts.	7	6	13
Mean	142.86	1141.7	603.85
SD	190.24	1646.3	1190.0
Median	100.00	500.00	400.00
Min : Max	-100.0 : 500.00	400.00 : 4500.0	-100.0 : 4500.0

Table 4.2.2 : Ultrafiltration (CA 125S, Proteins) and Uric acid - Screening visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
CA 125 (U.a./mL)			
no. pts.	7	5	12
Mean	54.60	37.96	47.67
SD	26.00	20.22	24.31
Median	54.60	23.60	46.35
Min : Max	29.90 : 106.30	22.80 : 60.80	22.80 : 106.30
Proteins in ultrafiltration (mg/L)			
no. pts.	7	5	12
Mean	1.80	2.16	1.95
SD	0.68	0.09	0.54
Median	2.20	2.20	2.20
Min : Max	0.80 : 2.20	2.00 : 2.20	0.80 : 2.20
Uric acid (mg/dL)			
no. pts.	7	6	13
Mean	4.31	5.20	4.72
SD	1.52	1.98	1.73
Median	4.50	4.70	4.50
Min : Max	1.90 : 6.60	3.30 : 8.90	1.90 : 8.90
Uric acid - Evaluation			
Normal	5 (71.4%)	4 (66.7%)	9 (69.2%)
Not Clinically Significant	2 (28.6%)	2 (33.3%)	4 (30.8%)

Table 5.1.1 : Hematology - Screening visit - Screened patients

	All No. pts (%)
RBC count (10^6/mmc)	
no. pts.	15
Mean	3.77
SD	0.39
Median	3.80
Min : Max	3.27 : 4.38
RBC count - Evaluation	
Not Clinically Significant	15(100.0%)
Hematocrit (%)	
no. pts.	15
Mean	34.72
SD	3.44
Median	35.10
Min : Max	29.20 : 40.20
Hematocrit - Evaluation	
Normal	4 (26.6%)
Not Clinically Significant	11 (73.3%)
Hemoglobin (gr/dL)	
no. pts.	15
Mean	11.21
SD	1.03
Median	11.30
Min : Max	9.20 : 12.60
Hemoglobin - Evaluation	
Not Clinically Significant	12 (80.0%)
Clinically significant for concomitant disease	1 (6.6%)
Clinically sign. for the pathology under study	2 (13.3%)

WBC count (10^3/uL)	
no. pts.	15
Mean	8.85
SD	6.87
Median	6.94
Min : Max	4.59 : 32.86
WBC count - Evaluation	
Normal	12 (80.0%)
Not Clinically Significant	3 (20.0%)

Neutrophils (10^3/uL)	
no. pts.	15
Mean	4.87
SD	1.81
Median	4.72
Min : Max	2.56 : 9.24
Neutrophils - Evaluation	
Normal	12 (80.0%)
Not Clinically Significant	3 (20.0%)

Table 5.1.2 : Hematology - Screening visit - Screened patients

	All No. pts (%)
Basophils (10^3/uL)	
no. pts.	15
Mean	0.05
SD	0.03
Median	0.05
Min : Max	0.01 : 0.11
Basophils - Evaluation	
Normal	14 (93.3%)
Not Clinically Significant	1 (6.6%)
Eosinophils (10^3/uL)	
no. pts.	15
Mean	0.23
SD	0.14
Median	0.24
Min : Max	0.00 : 0.53
Eosinophils - Evaluation	
Normal	13 (86.6%)
Not Clinically Significant	2 (13.3%)
Lymphocytes (10^3/uL)	
no. pts.	15
Mean	3.13
SD	6.90
Median	1.40
Min : Max	0.80 : 28.04
Lymphocytes - Evaluation	
Normal	9 (60.0%)
Not Clinically Significant	6 (40.0%)

Monocytes (10^3/uL)	
no. pts.	15
Mean	0.56
SD	0.17
Median	0.61
Min : Max	0.16 : 0.76

Monocytes - Evaluation	
Normal	14 (93.3%)
Not Clinically Significant	1 (6.6%)

Platelet count (10^3/mmc)	
no. pts.	15
Mean	216.00
SD	63.61
Median	225.00
Min : Max	116.00 : 367.00

Platelet count - Evaluation	
Normal	12 (80.0%)
Not Clinically Significant	3 (20.0%)

Table 5.2.1 : Hematology - Screening visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
RBC count (10^6/mmc)			
no. pts.	7	6	13
Mean	3.71	3.93	3.81
SD	0.45	0.33	0.40
Median	3.44	3.98	3.84
Min : Max	3.27 : 4.38	3.34 : 4.30	3.27 : 4.38
RBC count - Evaluation			
Not Clinically Significant	7(100.0%)	6(100.0%)	13(100.0%)
Hematocrit (%)			
no. pts.	7	6	13
Mean	34.16	35.90	34.96
SD	3.56	3.65	3.56
Median	33.10	36.45	35.40
Min : Max	29.50 : 40.20	29.20 : 39.90	29.20 : 40.20
Hematocrit - Evaluation			
Normal	2 (28.6%)	2 (33.3%)	4 (30.8%)
Not Clinically Significant	5 (71.4%)	4 (66.7%)	9 (69.2%)
Hemoglobin (gr/dL)			
no. pts.	7	6	13
Mean	10.93	11.50	11.19
SD	1.24	0.85	1.08
Median	10.60	11.85	11.30
Min : Max	9.20 : 12.60	9.90 : 12.20	9.20 : 12.60
Hemoglobin - Evaluation			
Not Clinically Significant	5 (71.4%)	5 (83.3%)	10 (76.9%)
Clinically significant for concomitant disease		1 (16.7%)	1 (7.7%)
Clinically sign. for the pathology under study	2 (28.6%)		2 (15.4%)

WBC count (10^3/uL)			
no. pts.	7	6	13
Mean	7.06	11.75	9.23
SD	2.29	10.43	7.34
Median	6.69	7.90	7.63
Min : Max	4.59 : 11.37	5.45 : 32.86	4.59 : 32.86
WBC count - Evaluation			
Normal	6 (85.7%)	5 (83.3%)	11 (84.6%)
Not Clinically Significant	1 (14.3%)	1 (16.7%)	2 (15.4%)

Neutrophils (10^3/uL)			
no. pts.	7	6	13
Mean	4.96	4.95	4.96
SD	2.23	1.73	1.93
Median	4.72	4.39	4.72
Min : Max	2.56 : 9.24	3.21 : 7.79	2.56 : 9.24
Neutrophils - Evaluation			
Normal	6 (85.7%)	5 (83.3%)	11 (84.6%)
Not Clinically Significant	1 (14.3%)	1 (16.7%)	2 (15.4%)

Table 5.2.2 : Hematology - Screening visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Basophils (10^3/uL)			
no. pts.	7	6	13
Mean	0.05	0.05	0.05
SD	0.02	0.04	0.03
Median	0.06	0.03	0.05
Min : Max	0.02 : 0.08	0.01 : 0.11	0.01 : 0.11
Basophils - Evaluation			
Normal	7(100.0%)	6(100.0%)	13(100.0%)
Eosinophils (10^3/uL)			
no. pts.	7	6	13
Mean	0.28	0.19	0.24
SD	0.12	0.16	0.15
Median	0.26	0.13	0.25
Min : Max	0.13 : 0.53	0.00 : 0.46	0.00 : 0.53
Eosinophils - Evaluation			
Normal	6 (85.7%)	6(100.0%)	12 (92.3%)
Not Clinically Significant	1 (14.3%)		1 (7.7%)
Lymphocytes (10^3/uL)			
no. pts.	7	6	13
Mean	1.19	5.97	3.40
SD	0.23	10.82	7.41
Median	1.21	1.60	1.40
Min : Max	0.80 : 1.43	0.86 : 28.04	0.80 : 28.04
Lymphocytes - Evaluation			
Normal	5 (71.4%)	4 (66.7%)	9 (69.2%)
Not Clinically Significant	2 (28.6%)	2 (33.3%)	4 (30.8%)
Monocytes (10^3/uL)			
no. pts.	7	6	13
Mean	0.57	0.59	0.58
SD	0.15	0.14	0.14
Median	0.61	0.65	0.61
Min : Max	0.33 : 0.76	0.35 : 0.72	0.33 : 0.76
Monocytes - Evaluation			
Normal	7(100.0%)	5 (83.3%)	12 (92.3%)
Not Clinically Significant		1 (16.7%)	1 (7.7%)

Platelet count (10^3/mmc)			
no. pts.	7	6	13
Mean	221.00	220.67	220.85
SD	54.33	84.42	66.67
Median	228.00	204.50	228.00
Min : Max	116.00 : 299.00	139.00 : 367.00	116.00 : 367.00
Platelet count - Evaluation			
Normal	6 (85.7%)	5 (83.3%)	11 (84.6%)
Not Clinically Significant	1 (14.3%)	1 (16.7%)	2 (15.4%)

Table 6.1.1 : Biochemistry - Screening visit - Screened patients

	All No. pts (%)
BUN (mg/dL)	
no. pts.	15
Mean	92.54
SD	37.89
Median	81.77
Min : Max	52.00 : 194.00
BUN - Evaluation	
Not Clinically Significant	9 (60.0%)
Clinically significant for concomitant disease	3 (20.0%)
Clinically sign. for the pathology under study	3 (20.0%)
Creatinine (mg/dL)	
no. pts.	15
Mean	8.26
SD	1.73
Median	7.85
Min : Max	6.25 : 12.35
Creatinine - Evaluation	
Not Clinically Significant	9 (60.0%)
Clinically significant for concomitant disease	3 (20.0%)
Clinically sign. for the pathology under study	3 (20.0%)
Glucose (mg/dL)	
no. pts.	15
Mean	104.20
SD	37.86
Median	90.00
Min : Max	60.00 : 199.00
Glucose - Evaluation	
Normal	8 (53.3%)
Not Clinically Significant	7 (46.6%)

Total Cholesterol (mg/dL)	
no. pts.	14
Mean	161.93
SD	37.04
Median	158.50
Min : Max	108.00 : 237.00

Total Cholesterol - Evaluation	
Normal	11 (78.5%)
Not Clinically Significant	3 (21.4%)

HDL Cholesterol (mg/dL)	
no. pts.	13
Mean	44.15
SD	21.76
Median	37.00
Min : Max	25.00 : 102.00

HDL Cholesterol - Evaluation	
Normal	4 (30.7%)
Not Clinically Significant	9 (69.2%)

Table 6.1.2 : Biochemistry - Screening visit - Screened patients

	All No. pts (%)
LDL Cholesterol (mg/dL)	
no. pts.	13
Mean	80.14
SD	26.96
Median	73.00
Min : Max	47.00 : 149.00
LDL Cholesterol - Evaluation	
Normal	12 (92.3%)
Not Clinically Significant	1 (7.6%)
Triglycerides (mg/dL)	
no. pts.	14
Mean	181.86
SD	131.21
Median	125.50
Min : Max	55.00 : 521.00
Triglycerides - Evaluation	
Normal	7 (50.0%)
Not Clinically Significant	7 (50.0%)
Total proteins (g/dL)	
no. pts.	15
Mean	6.46
SD	0.51
Median	6.30
Min : Max	5.70 : 7.50
Total proteins - Evaluation	
Normal	7 (46.6%)
Not Clinically Significant	8 (53.3%)

Albumin (g/dL)	
no. pts.	15
Mean	3.58
SD	0.58
Median	3.81
Min : Max	2.40 : 4.34
Albumin - Evaluation	
Normal	9 (60.0%)
Not Clinically Significant	6 (40.0%)

Total Bilirubin (mg/dL)	
no. pts.	12
Mean	0.52
SD	0.18
Median	0.51
Min : Max	0.30 : 0.96
Total Bilirubin - Evaluation	
Normal	12(100.0%)

Table 6.1.3 : Biochemistry - Screening visit - Screened patients

	All No. pts (%)
SGOT (AST) (U/L)	
no. pts.	15
Mean	17.00
SD	5.42
Median	16.00
Min : Max	8.00 : 32.00
SGOT (AST) - Evaluation	
Normal	12 (80.0%)
Not Clinically Significant	3 (20.0%)
SGPT (ALT) (U/L)	
no. pts.	15
Mean	16.40
SD	6.37
Median	17.00
Min : Max	8.00 : 35.00
SGPT (ALT - Evaluation	
Normal	13 (86.6%)
Not Clinically Significant	2 (13.3%)
Alkaline Phosphatase (U/L)	
no. pts.	15
Mean	86.00
SD	38.81
Median	72.00
Min : Max	47.00 : 163.00
Alkaline Phosphatase - Evaluation	
Normal	11 (73.3%)
Not Clinically Significant	4 (26.6%)

GGT (U/L)	
no. pts.	15
Mean	23.87
SD	19.87
Median	15.00
Min : Max	8.00 : 74.00
GGT - Evaluation	
Normal	10 (66.6%)
Not Clinically Significant	5 (33.3%)

Serum Sodium (mmol/L)	
no. pts.	15
Mean	138.60
SD	3.09
Median	138.00
Min : Max	132.00 : 143.00
Serum Sodium - Evaluation	
Normal	13 (86.6%)
Not Clinically Significant	2 (13.3%)

Table 6.1.4 : Biochemistry - Screening visit - Screened patients

	All No. pts (%)
Potassium (mmol/L)	
no. pts.	15
Mean	4.61
SD	0.54
Median	4.72
Min : Max	3.52 : 5.45
Potassium - Evaluation	
Normal	12 (80.0%)
Not Clinically Significant	3 (20.0%)
Calcium (mmol/L)	
no. pts.	15
Mean	2.24
SD	0.17
Median	2.20
Min : Max	1.90 : 2.50
Calcium - Evaluation	
Normal	12 (80.0%)
Not Clinically Significant	2 (13.3%)
Clinically sign. for the pathology under study	1 (6.6%)
Phosphorus (mmol/L)	
no. pts.	15
Mean	1.68
SD	0.38
Median	1.74
Min : Max	0.81 : 2.26
Phosphorus - Evaluation	
Normal	2 (13.3%)
Not Clinically Significant	9 (60.0%)
Clinically significant for concomitant disease	1 (6.6%)
Clinically sign. for the pathology under study	3 (20.0%)

Table 6.2.1 : Biochemistry - Screening visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BUN (mg/dL)			
no. pts.	7	6	13
Mean	76.37	119.08	96.08
SD	13.38	48.68	39.60
Median	81.77	103.10	83.70
Min : Max	52.00 : 91.12	75.50 : 194.00	52.00 : 194.00
BUN - Evaluation			
Not Clinically Significant	4 (57.1%)	5 (83.3%)	9 (69.2%)
Clinically significant for concomitant disease		1 (16.7%)	1 (7.7%)
Clinically sign. for the pathology under study	3 (42.9%)		3 (23.1%)
Creatinine (mg/dL)			
no. pts.	7	6	13
Mean	7.35	9.00	8.11
SD	0.71	2.31	1.79
Median	7.24	8.47	7.78
Min : Max	6.25 : 8.23	6.57 : 12.35	6.25 : 12.35
Creatinine - Evaluation			
Not Clinically Significant	4 (57.1%)	5 (83.3%)	9 (69.2%)
Clinically significant for concomitant disease		1 (16.7%)	1 (7.7%)
Clinically sign. for the pathology under study	3 (42.9%)		3 (23.1%)
Glucose (mg/dL)			
no. pts.	7	6	13
Mean	108.86	111.33	110.00
SD	44.18	31.53	37.31
Median	93.00	95.00	93.00
Min : Max	75.00 : 199.00	87.00 : 155.00	75.00 : 199.00
Glucose - Evaluation			
Normal	4 (57.1%)	4 (66.7%)	8 (61.5%)
Not Clinically Significant	3 (42.9%)	2 (33.3%)	5 (38.5%)

Total Cholesterol (mg/dL)			
no. pts.	7	5	12
Mean	175.29	150.00	164.75
SD	46.00	23.22	38.99
Median	172.00	147.00	159.00
Min : Max	108.00 : 237.00	123.00 : 185.00	108.00 : 237.00
Total Cholesterol - Evaluation			
Normal	5 (71.4%)	5(100.0%)	10 (83.3%)
Not Clinically Significant	2 (28.6%)		2 (16.7%)

HDL Cholesterol (mg/dL)			
no. pts.	7	4	11
Mean	34.86	46.00	38.91
SD	8.13	20.99	14.27
Median	32.00	41.50	33.00
Min : Max	25.00 : 48.00	26.00 : 75.00	25.00 : 75.00
HDL Cholesterol - Evaluation			
Normal	2 (28.6%)	2 (50.0%)	4 (36.4%)
Not Clinically Significant	5 (71.4%)	2 (50.0%)	7 (63.6%)

Table 6.2.2 : Biochemistry - Screening visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
LDL Cholesterol (mg/dL)			
no. pts.	7	4	11
Mean	94.66	64.80	83.80
SD	28.59	9.14	27.24
Median	95.00	64.60	75.20
Min : Max	59.40 : 149.00	54.80 : 75.20	54.80 : 149.00
LDL Cholesterol - Evaluation			
Normal	7(100.0%)	4(100.0%)	11(100.0%)
Triglycerides (mg/dL)			
no. pts.	7	5	12
Mean	230.57	162.40	202.17
SD	147.24	106.65	131.12
Median	238.00	108.00	167.00
Min : Max	83.00 : 521.00	84.00 : 331.00	83.00 : 521.00
Triglycerides - Evaluation			
Normal	3 (42.9%)	3 (60.0%)	6 (50.0%)
Not Clinically Significant	4 (57.1%)	2 (40.0%)	6 (50.0%)
Total proteins (g/dL)			
no. pts.	7	6	13
Mean	6.69	6.20	6.46
SD	0.54	0.36	0.51
Median	6.40	6.20	6.30
Min : Max	6.10 : 7.50	5.70 : 6.80	5.70 : 7.50
Total proteins - Evaluation			
Normal	5 (71.4%)	2 (33.3%)	7 (53.8%)
Not Clinically Significant	2 (28.6%)	4 (66.7%)	6 (46.2%)

Albumin (g/dL)			
no. pts.	7	6	13
Mean	3.61	3.55	3.58
SD	0.56	0.69	0.60
Median	3.85	3.76	3.81
Min : Max	2.51 : 4.09	2.40 : 4.34	2.40 : 4.34
Albumin - Evaluation			
Normal	5 (71.4%)	4 (66.7%)	9 (69.2%)
Not Clinically Significant	2 (28.6%)	2 (33.3%)	4 (30.8%)

Total Bilirubin (mg/dL)			
no. pts.	7	5	12
Mean	0.49	0.55	0.52
SD	0.10	0.27	0.18
Median	0.47	0.55	0.51
Min : Max	0.33 : 0.62	0.30 : 0.96	0.30 : 0.96
Total Bilirubin - Evaluation			
Normal	7(100.0%)	5(100.0%)	12(100.0%)

Table 6.2.3 : Biochemistry - Screening visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
SGOT (AST) (U/L)			
no. pts.	7	6	13
Mean	18.00	18.00	18.00
SD	3.06	7.01	5.02
Median	18.00	15.00	17.00
Min : Max	13.00 : 22.00	14.00 : 32.00	13.00 : 32.00
SGOT (AST) - Evaluation			
Normal	7(100.0%)	4 (66.7%)	11 (84.6%)
Not Clinically Significant		2 (33.3%)	2 (15.4%)
SGPT (ALT) (U/L)			
no. pts.	7	6	13
Mean	14.29	19.00	16.46
SD	4.35	8.37	6.68
Median	13.00	17.00	17.00
Min : Max	8.00 : 21.00	10.00 : 35.00	8.00 : 35.00
SGPT (ALT - Evaluation			
Normal	7(100.0%)	5 (83.3%)	12 (92.3%)
Not Clinically Significant		1 (16.7%)	1 (7.7%)
Alkaline Phosphatase (U/L)			
no. pts.	7	6	13
Mean	63.00	104.33	82.08
SD	16.19	43.31	37.05
Median	53.00	100.00	72.00
Min : Max	47.00 : 85.00	61.00 : 163.00	47.00 : 163.00
Alkaline Phosphatase - Evaluation			
Normal	7(100.0%)	4 (66.7%)	11 (84.6%)
Not Clinically Significant		2 (33.3%)	2 (15.4%)

GGT (U/L)			
no. pts.	7	6	13
Mean	26.29	25.17	25.77
SD	19.34	24.09	20.72
Median	19.00	14.50	19.00
Min : Max	10.00 : 66.00	13.00 : 74.00	10.00 : 74.00
GGT - Evaluation			
Normal	6 (85.7%)	3 (50.0%)	9 (69.2%)
Not Clinically Significant	1 (14.3%)	3 (50.0%)	4 (30.8%)

Serum Sodium (mmol/L)			
no. pts.	7	6	13
Mean	139.14	137.50	138.38
SD	2.85	3.27	3.04
Median	140.00	137.50	138.00
Min : Max	136.00 : 143.00	132.00 : 142.00	132.00 : 143.00
Serum Sodium - Evaluation			
Normal	7(100.0%)	5 (83.3%)	12 (92.3%)
Not Clinically Significant		1 (16.7%)	1 (7.7%)

Table 6.2.4 : Biochemistry - Screening visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Potassium (mmol/L)			
no. pts.	7	6	13
Mean	4.66	4.70	4.68
SD	0.52	0.60	0.54
Median	4.77	4.61	4.73
Min : Max	3.52 : 5.03	4.00 : 5.45	3.52 : 5.45
Potassium - Evaluation			
Normal	7(100.0%)	4 (66.7%)	11 (84.6%)
Not Clinically Significant		2 (33.3%)	2 (15.4%)
Calcium (mmol/L)			
no. pts.	7	6	13
Mean	2.23	2.22	2.23
SD	0.16	0.21	0.17
Median	2.30	2.20	2.20
Min : Max	1.90 : 2.40	1.92 : 2.50	1.90 : 2.50
Calcium - Evaluation			
Normal	6 (85.7%)	5 (83.3%)	11 (84.6%)
Not Clinically Significant		1 (16.7%)	1 (7.7%)
Clinically sign. for the pathology under study	1 (14.3%)		1 (7.7%)
Phosphorus (mmol/L)			
no. pts.	7	6	13
Mean	1.80	1.61	1.71
SD	0.28	0.51	0.39
Median	1.74	1.70	1.74
Min : Max	1.40 : 2.20	0.81 : 2.26	0.81 : 2.26
Phosphorus - Evaluation			
Normal	1 (14.3%)	1 (16.7%)	2 (15.4%)
Not Clinically Significant	3 (42.9%)	4 (66.7%)	7 (53.8%)
Clinically significant for concomitant disease		1 (16.7%)	1 (7.7%)
Clinically sign. for the pathology under study	3 (42.9%)		3 (23.1%)

Table 7 : Clinical parameters - Day-0 visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Weight (kg)			
no. pts.	7	6	13
Mean	78.57	81.15	79.76
SD	16.67	13.14	14.58
Median	78.50	85.00	84.00
Min : Max	53.00 : 97.00	63.40 : 98.00	53.00 : 98.00
Systolic Blood Pressure (mmHg)			
no. pts.	7	6	13
Mean	137.86	131.67	135.00
SD	22.52	14.72	18.82
Median	145.00	135.00	140.00
Min : Max	110.00 : 165.00	110.00 : 150.00	110.00 : 165.00
Diastolic Blood Pressure (mmHg)			
no. pts.	7	6	13
Mean	81.43	78.33	80.00
SD	7.48	10.33	8.66
Median	80.00	80.00	80.00
Min : Max	70.00 : 95.00	65.00 : 95.00	65.00 : 95.00
Heart Rate (beats/min)			
no. pts.	7	6	13
Mean	65.57	76.50	70.62
SD	9.52	11.81	11.64
Median	67.00	76.00	73.00
Min : Max	50.00 : 75.00	56.00 : 90.00	50.00 : 90.00
Diuresis (L/day)			
no. pts.	7	6	13
Mean	1.68	1.62	1.65
SD	0.59	0.68	0.61
Median	1.60	1.93	1.75
Min : Max	1.10 : 2.70	0.55 : 2.20	0.55 : 2.70
Does the patient show hyperhydratation signs?			
No	7(100.0%)	6(100.0%)	13(100.0%)

Table 8 : Subjective quetionnaire and Efficacy end-points - Day-0 visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Did the patient fill in the subjective questionnaire?			
Yes	7(100.0%)	6(100.0%)	13(100.0%)
Total score			
no. pts.	7	6	13
Mean	18.57	17.50	18.08
SD	3.78	2.51	3.17
Median	17.00	17.00	17.00
Min : Max	14.00 : 25.00	15.00 : 21.00	14.00 : 25.00
WEEKLY TOTAL UREA Kt/V			
no. pts.	7	6	13
Mean	1.29	1.27	1.28
SD	0.26	0.29	0.26
Median	1.24	1.30	1.24
Min : Max	0.95 : 1.68	0.76 : 1.59	0.76 : 1.68
PERITONEAL EQUILIBRATION TEST (PET) - Dialysate/Plasma creatinine			
no. pts.	7	6	13
Mean	0.53	0.64	0.58
SD	0.15	0.07	0.13
Median	0.57	0.64	0.61
Min : Max	0.22 : 0.63	0.53 : 0.71	0.22 : 0.71
WEEKLY TOTAL CREATININE CLEARANCE			
no. pts.	7	6	13
Mean	70.13	63.40	67.02
SD	17.77	15.05	16.26
Median	77.76	62.04	62.62
Min : Max	50.03 : 93.39	43.28 : 86.94	43.28 : 93.39

Table 9.1 : Ultrafiltration - Day-0 visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
1st Daily Bag (mL)			
no. pts.	7	6	13
Mean	135.71	425.00	269.23
SD	143.51	571.62	411.06
Median	100.00	125.00	100.00
Min : Max	0.00 : 300.00	50.00 : 1500.0	0.00 : 1500.0
2nd Daily Bag (mL)			
no. pts.	7	6	13
Mean	0.00	16.67	7.69
SD	0.00	112.55	73.16
Median	0.00	50.00	0.00
Min : Max	0.00 : 0.00	-200.0 : 100.00	-200.0 : 100.00
3rd Daily Bag (mL)			
no. pts.	7	6	13
Mean	0.00	0.00	0.00
SD	0.00	0.00	0.00
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00
Nocturnal Bag (mL)			
no. pts.	7	6	13
Mean	14.29	108.33	57.69
SD	37.80	146.34	109.63
Median	0.00	175.00	0.00
Min : Max	0.00 : 100.00	-100.0 : 250.00	-100.0 : 250.00
Total ultrafiltration (mL)			
no. pts.	7	6	13
Mean	150.00	550.00	334.62
SD	132.29	467.97	378.26
Median	100.00	400.00	300.00
Min : Max	0.00 : 300.00	300.00 : 1500.0	0.00 : 1500.0

Table 9.2 : Ultrafiltration (CA 125S, Proteins), Uric acid and Lactic acid - Day-0 visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
CA 125 (U.a./mL)			
no. pts.	7	5	12
Mean	72.00	44.52	60.55
SD	51.53	30.27	44.51
Median	52.60	45.50	49.40
Min : Max	35.90 : 184.00	9.90 : 88.60	9.90 : 184.00
Proteins in ultrafiltration (mg/L)			
no. pts.	7	5	12
Mean	0.80	0.98	0.88
SD	0.00	0.72	0.44
Median	0.80	0.80	0.80
Min : Max	0.80 : 0.80	0.30 : 2.20	0.30 : 2.20
Uric acid (mg/dL)			
no. pts.	7	5	12
Mean	5.73	4.40	5.18
SD	2.00	0.73	1.68
Median	4.80	4.40	4.65
Min : Max	4.30 : 9.90	3.30 : 5.20	3.30 : 9.90
Uric acid - Evaluation			
Normal	5 (71.4%)	4 (66.7%)	9 (69.2%)
Not Clinically Significant	2 (28.6%)	1 (16.7%)	3 (23.1%)
Missing data		1 (16.7%)	1 (7.7%)
Lactic acid (mg/dL)			
no. pts.	7	6	13
Mean	10.47	6.63	8.70
SD	4.86	5.73	5.43
Median	9.00	6.00	8.10
Min : Max	7.00 : 21.00	0.70 : 15.30	0.70 : 21.00
Lactic acid - Evaluation			
Normal	2 (28.6%)	4 (66.7%)	6 (46.2%)
Not Clinically Significant	5 (71.4%)	2 (33.3%)	7 (53.8%)

Table 10.1 : Hematology - Day-0 visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
RBC count (10^6/mmc)			
no. pts.	7	6	13
Mean	3.76	3.88	3.82
SD	0.48	0.46	0.45
Median	3.71	3.99	3.91
Min : Max	3.07 : 4.48	3.03 : 4.31	3.03 : 4.48
RBC count - Evaluation			
Not Clinically Significant	7(100.0%)	6(100.0%)	13(100.0%)
Hematocrit (%)			
no. pts.	7	6	13
Mean	34.57	35.23	34.88
SD	4.38	4.32	4.18
Median	35.10	35.85	35.60
Min : Max	27.60 : 42.00	26.90 : 39.10	26.90 : 42.00
Hematocrit - Evaluation			
Normal	1 (14.3%)	2 (33.3%)	3 (23.1%)
Not Clinically Significant	6 (85.7%)	4 (66.7%)	10 (76.9%)
Hemoglobin (gr/dL)			
no. pts.	7	6	13
Mean	11.04	11.22	11.12
SD	1.43	1.18	1.27
Median	11.30	11.55	11.50
Min : Max	8.50 : 13.20	8.90 : 12.20	8.50 : 13.20
Hemoglobin - Evaluation			
Normal	1 (14.3%)		1 (7.7%)
Not Clinically Significant	6 (85.7%)	6(100.0%)	12 (92.3%)
WBC count (10^3/uL)			
no. pts.	7	6	13
Mean	7.25	11.49	9.21
SD	3.47	9.93	7.21
Median	6.01	8.23	6.52
Min : Max	4.28 : 14.27	4.19 : 31.21	4.19 : 31.21

WBC count - Evaluation			
Normal	6 (85.7%)	4 (66.7%)	10 (76.9%)
Not Clinically Significant	1 (14.3%)	2 (33.3%)	3 (23.1%)
Neutrophils (10^3/uL)			
no. pts.	7	6	13
Mean	5.16	4.88	5.03
SD	3.04	2.26	2.60
Median	4.42	4.54	4.42
Min : Max	2.52 : 11.35	2.10 : 8.67	2.10 : 11.35
Neutrophils - Evaluation			
Normal	6 (85.7%)	5 (83.3%)	11 (84.6%)
Not Clinically Significant	1 (14.3%)	1 (16.7%)	2 (15.4%)

Table 10.2 : Hematology - Day-0 visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Basophils (10^3/uL)			
no. pts.	7	6	13
Mean	0.05	0.05	0.05
SD	0.02	0.03	0.02
Median	0.04	0.04	0.04
Min : Max	0.01 : 0.07	0.01 : 0.09	0.01 : 0.09
Basophils - Evaluation			
Normal	7(100.0%)	6(100.0%)	13(100.0%)
Eosinophils (10^3/uL)			
no. pts.	7	6	13
Mean	0.33	0.15	0.25
SD	0.19	0.11	0.18
Median	0.26	0.18	0.19
Min : Max	0.14 : 0.65	0.00 : 0.31	0.00 : 0.65
Eosinophils - Evaluation			
Normal	5 (71.4%)	6(100.0%)	11 (84.6%)
Not Clinically Significant	2 (28.6%)		2 (15.4%)
Lymphocytes (10^3/uL)			
no. pts.	7	6	13
Mean	1.09	5.76	3.24
SD	0.25	10.28	7.07
Median	1.18	1.52	1.27
Min : Max	0.69 : 1.38	1.24 : 26.73	0.69 : 26.73
Lymphocytes - Evaluation			
Normal	4 (57.1%)	4 (66.7%)	8 (61.5%)
Not Clinically Significant	3 (42.9%)	2 (33.3%)	5 (38.5%)
Monocytes (10^3/uL)			
no. pts.	7	6	13
Mean	0.62	0.65	0.64
SD	0.23	0.18	0.20
Median	0.57	0.64	0.57
Min : Max	0.30 : 1.02	0.48 : 0.88	0.30 : 1.02

Monocytes - Evaluation			
Normal	6 (85.7%)	5 (83.3%)	11 (84.6%)
Not Clinically Significant	1 (14.3%)	1 (16.7%)	2 (15.4%)
Platelet count (10^3/mmc)			
no. pts.	7	6	13
Mean	224.43	225.50	224.92
SD	63.82	77.98	67.60
Median	225.00	225.00	225.00
Min : Max	117.00 : 301.00	132.00 : 349.00	117.00 : 349.00
Platelet count - Evaluation			
Normal	6 (85.7%)	5 (83.3%)	11 (84.6%)
Not Clinically Significant	1 (14.3%)	1 (16.7%)	2 (15.4%)

Table 11.1 : Biochemistry - Day-0 visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BUN (mg/dL)			
no. pts.	7	6	13
Mean	160.74	168.45	164.30
SD	52.63	48.12	48.64
Median	164.00	173.00	169.00
Min : Max	74.20 : 230.00	79.70 : 219.00	74.20 : 230.00
BUN - Evaluation			
Not Clinically Significant	7(100.0%)	6(100.0%)	13(100.0%)
Creatinine (mg/dL)			
no. pts.	7	6	13
Mean	7.70	9.04	8.32
SD	1.74	2.19	2.00
Median	8.26	8.12	8.25
Min : Max	5.64 : 9.96	6.97 : 12.83	5.64 : 12.83
Creatinine - Evaluation			
Not Clinically Significant	7(100.0%)	6(100.0%)	13(100.0%)
Glucose (mg/dL)			
no. pts.	7	6	13
Mean	106.71	114.50	110.31
SD	28.99	26.64	27.06
Median	98.00	116.00	98.00
Min : Max	71.00 : 148.00	87.00 : 141.00	71.00 : 148.00
Glucose - Evaluation			
Normal	3 (42.9%)	3 (50.0%)	6 (46.2%)
Not Clinically Significant	4 (57.1%)	3 (50.0%)	7 (53.8%)

Total Cholesterol (mg/dL)			
no. pts.	7	6	13
Mean	161.71	137.83	150.69
SD	31.24	15.01	27.12
Median	166.00	138.00	149.00
Min : Max	102.00 : 196.00	113.00 : 156.00	102.00 : 196.00
Total Cholesterol - Evaluation			
Normal	7(100.0%)	6(100.0%)	13(100.0%)

HDL Cholesterol (mg/dL)			
no. pts.	7	6	13
Mean	37.00	47.00	41.62
SD	10.42	17.56	14.48
Median	35.00	45.50	39.00
Min : Max	25.00 : 52.00	25.00 : 78.00	25.00 : 78.00
HDL Cholesterol - Evaluation			
Normal	2 (28.6%)	4 (66.7%)	6 (46.2%)
Not Clinically Significant	5 (71.4%)	2 (33.3%)	7 (53.8%)

Table 11.2 : Biochemistry - Day-0 visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
LDL Cholesterol (mg/dL)			
no. pts.	7	6	13
Mean	90.14	65.83	78.92
SD	22.53	11.51	21.64
Median	97.00	72.00	73.00
Min : Max	50.00 : 114.00	47.00 : 75.00	47.00 : 114.00
LDL Cholesterol - Evaluation			
Normal	4 (57.1%)	5 (83.3%)	9 (69.2%)
Not Clinically Significant	3 (42.9%)	1 (16.7%)	4 (30.8%)
Triglycerides (mg/dL)			
no. pts.	6	6	12
Mean	153.33	128.67	141.00
SD	106.53	48.25	79.89
Median	118.50	122.50	118.50
Min : Max	83.00 : 364.00	77.00 : 189.00	77.00 : 364.00
Triglycerides - Evaluation			
Normal	4 (66.7%)	4 (66.7%)	8 (66.7%)
Not Clinically Significant	2 (33.3%)	2 (33.3%)	4 (33.3%)
Total proteins (g/dL)			
no. pts.	7	6	13
Mean	6.53	6.10	6.33
SD	0.51	0.51	0.54
Median	6.50	6.10	6.50
Min : Max	5.90 : 7.30	5.50 : 6.70	5.50 : 7.30
Total proteins - Evaluation			
Normal	5 (71.4%)	3 (50.0%)	8 (61.5%)
Not Clinically Significant	2 (28.6%)	3 (50.0%)	5 (38.5%)

Albumin (g/dL)			
no. pts.	7	6	13
Mean	3.71	3.36	3.55
SD	0.17	0.73	0.52
Median	3.60	3.55	3.60
Min : Max	3.60 : 4.00	2.00 : 4.10	2.00 : 4.10
Albumin - Evaluation			
Normal	7(100.0%)	4 (66.7%)	11 (84.6%)
Not Clinically Significant		2 (33.3%)	2 (15.4%)

Total Bilirubin (mg/dL)			
no. pts.	7	4	11
Mean	0.45	0.61	0.51
SD	0.10	0.26	0.18
Median	0.43	0.64	0.50
Min : Max	0.35 : 0.61	0.30 : 0.86	0.30 : 0.86
Total Bilirubin - Evaluation			
Normal	7(100.0%)	4(100.0%)	11(100.0%)

Table 11.3 : Biochemistry - Day-0 visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
SGOT (AST) (U/L)			
no. pts.	7	5	12
Mean	12.57	14.60	13.42
SD	3.60	4.77	4.06
Median	14.00	15.00	14.50
Min : Max	7.00 : 17.00	8.00 : 20.00	7.00 : 20.00
SGOT (AST) - Evaluation			
Normal	7(100.0%)	4 (80.0%)	11 (91.7%)
Not Clinically Significant		1 (20.0%)	1 (8.3%)
SGPT (ALT) (U/L)			
no. pts.	7	5	12
Mean	14.29	15.80	14.92
SD	4.96	6.98	5.63
Median	13.00	16.00	13.50
Min : Max	9.00 : 24.00	9.00 : 27.00	9.00 : 27.00
SGPT (ALT - Evaluation			
Normal	7(100.0%)	4 (80.0%)	11 (91.7%)
Not Clinically Significant		1 (20.0%)	1 (8.3%)
Alkaline Phosphatase (U/L)			
no. pts.	7	5	12
Mean	72.71	100.60	84.33
SD	22.54	41.47	33.30
Median	67.00	82.00	74.50
Min : Max	53.00 : 112.00	64.00 : 167.00	53.00 : 167.00
Alkaline Phosphatase - Evaluation			
Normal	7(100.0%)	4 (80.0%)	11 (91.7%)
Not Clinically Significant		1 (20.0%)	1 (8.3%)

GGT (U/L)			
no. pts.	7	5	12
Mean	23.71	15.00	20.08
SD	12.38	2.24	10.27
Median	25.00	15.00	16.00
Min : Max	10.00 : 44.00	12.00 : 18.00	10.00 : 44.00
GGT - Evaluation			
Normal	7(100.0%)	4 (80.0%)	11 (91.7%)
Not Clinically Significant		1 (20.0%)	1 (8.3%)

Serum Sodium (mmol/L)			
no. pts.	7	6	13
Mean	138.00	137.17	137.62
SD	2.08	5.42	3.82
Median	138.00	139.00	138.00
Min : Max	135.00 : 141.00	130.00 : 143.00	130.00 : 143.00
Serum Sodium - Evaluation			
Normal	6 (85.7%)	4 (66.7%)	10 (76.9%)
Not Clinically Significant	1 (14.3%)	2 (33.3%)	3 (23.1%)

Table 11.4 : Biochemistry - Day-0 visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Potassium (mmol/L)			
no. pts.	7	6	13
Mean	4.57	4.56	4.57
SD	0.58	0.67	0.59
Median	4.60	4.65	4.60
Min : Max	3.40 : 5.20	3.50 : 5.37	3.40 : 5.37
Potassium - Evaluation			
Normal	5 (71.4%)	5 (83.3%)	10 (76.9%)
Not Clinically Significant	2 (28.6%)	1 (16.7%)	3 (23.1%)
Calcium (mmol/L)			
no. pts.	7	6	13
Mean	2.30	2.20	2.25
SD	0.33	0.24	0.29
Median	2.22	2.21	2.22
Min : Max	1.97 : 2.97	1.82 : 2.50	1.82 : 2.97
Calcium - Evaluation			
Normal	3 (42.9%)	4 (66.7%)	7 (53.8%)
Not Clinically Significant	4 (57.1%)	2 (33.3%)	6 (46.2%)
Phosphorus (mmol/L)			
no. pts.	7	6	13
Mean	1.74	1.69	1.72
SD	0.26	0.29	0.26
Median	1.84	1.59	1.70
Min : Max	1.32 : 2.03	1.42 : 2.13	1.32 : 2.13
Phosphorus - Evaluation			
Normal	1 (14.3%)	1 (16.7%)	2 (15.4%)
Not Clinically Significant	6 (85.7%)	5 (83.3%)	11 (84.6%)

Table 12.1 : Electrocardiogram (ECG) - Day-0 visit - Enrolled patients

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Is the ECG normal?			
Yes	3 (42.8%)	5 (83.3%)	8 (61.5%)
No	4 (57.1%)	1 (16.6%)	5 (38.4%)

Table 12.2: ECG test at Day-0 visit - details

Treatment group	Patient no.	ECG test	Clinical evaluation
Group A	01-005	Sinus Bradycardia	Not Clinically Significant
	01-006	Sinus Bradycardia	Not Clinically Significant
	01-007	Left Bundle Branch Block	Not Clinically Significant
	01-009	Sinus rhythm, previous lower myocardial infarction	Not Clinically Significant
Group B	01-001	Sinus Bradycardia	Not Clinically Significant

Table 13 : Clinical parameters - Intervention period - Weight - Changes vs Day-0 visit - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	6	12
Mean	76.50	81.15	78.83
SD	17.25	13.14	14.82
Median	74.50	85.00	81.25
Min : Max	53.00 : 97.00	63.40 : 98.00	53.00 : 98.00
Day-14 visit			
no. pts.	6	6	12
Mean	76.75	81.12	78.93
SD	17.70	13.98	15.38
Median	77.00	84.50	81.50
Min : Max	50.50 : 97.00	62.70 : 100.00	50.50 : 100.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.25	-0.03	0.11
SD	1.97	1.66	1.74
Median	0.00	-0.60	-0.25
Min : Max	-2.50 : 2.50	-2.00 : 2.00	-2.50 : 2.50
Day-28 visit			
no. pts.	6	6	12
Mean	75.17	80.87	78.02
SD	17.44	12.87	14.91
Median	75.75	84.00	82.00
Min : Max	49.00 : 96.50	62.70 : 98.00	49.00 : 98.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-1.33	-0.28	-0.81
SD	2.64	2.03	2.31
Median	-0.75	0.00	-0.25
Min : Max	-5.00 : 1.50	-4.00 : 1.50	-5.00 : 1.50

Table 14 : Clinical parameters - Intervention period - Systolic BP - Changes vs Day-0 visit - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	6	12
Mean	134.17	131.67	132.92
SD	22.23	14.72	18.02
Median	132.50	135.00	135.00
Min : Max	110.00 : 165.00	110.00 : 150.00	110.00 : 165.00
Day-14 visit			
no. pts.	6	6	12
Mean	145.00	138.17	141.58
SD	17.61	9.85	14.06
Median	150.00	137.50	145.50
Min : Max	120.00 : 170.00	128.00 : 150.00	120.00 : 170.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	10.83	6.50	8.67
SD	24.78	16.80	20.31
Median	15.00	5.00	7.50
Min : Max	-20.00 : 40.00	-12.00 : 36.00	-20.00 : 40.00
Day-28 visit			
no. pts.	6	6	12
Mean	135.00	132.50	133.75
SD	16.73	15.08	15.24
Median	137.50	135.00	135.00
Min : Max	105.00 : 150.00	105.00 : 150.00	105.00 : 150.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.83	0.83	0.83
SD	21.31	10.68	16.07
Median	-7.50	0.00	-5.00
Min : Max	-15.00 : 40.00	-10.00 : 15.00	-15.00 : 40.00

Table 15 : Clinical parameters - Intervention period - Diastolic BP - Changes vs Day-0 visit - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	6	12
Mean	81.67	78.33	80.00
SD	8.16	10.33	9.05
Median	80.00	80.00	80.00
Min : Max	70.00 : 95.00	65.00 : 95.00	65.00 : 95.00
Day-14 visit			
no. pts.	6	6	12
Mean	75.83	77.50	76.67
SD	12.01	9.87	10.52
Median	80.00	75.00	80.00
Min : Max	55.00 : 90.00	70.00 : 95.00	55.00 : 95.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-5.83	-0.83	-3.33
SD	15.30	8.01	11.93
Median	-7.50	0.00	-2.50
Min : Max	-25.00 : 20.00	-10.00 : 10.00	-25.00 : 20.00
Day-28 visit			
no. pts.	6	6	12
Mean	80.00	80.83	80.42
SD	8.37	12.01	9.88
Median	77.50	80.00	80.00
Min : Max	70.00 : 90.00	60.00 : 95.00	60.00 : 95.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-1.67	2.50	0.42
SD	9.83	12.94	11.17
Median	-5.00	5.00	-2.50
Min : Max	-15.00 : 10.00	-15.00 : 15.00	-15.00 : 15.00

Table 16 : Clinical parameters - Intervention period - Heart Rate - Changes vs Day-0 visit - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	6	12
Mean	64.50	76.50	70.50
SD	9.95	11.81	12.15
Median	67.00	76.00	74.00
Min : Max	50.00 : 75.00	56.00 : 90.00	50.00 : 90.00
Day-14 visit			
no. pts.	6	6	12
Mean	63.33	77.17	70.25
SD	9.14	17.36	15.07
Median	62.50	77.50	64.50
Min : Max	51.00 : 79.00	53.00 : 96.00	51.00 : 96.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-1.17	0.67	-0.25
SD	9.72	14.29	11.69
Median	0.50	1.50	1.50
Min : Max	-16.00 : 10.00	-23.00 : 21.00	-23.00 : 21.00
Day-28 visit			
no. pts.	6	6	12
Mean	66.50	71.67	69.08
SD	11.84	15.24	13.29
Median	68.50	76.00	69.50
Min : Max	53.00 : 85.00	48.00 : 85.00	48.00 : 85.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	2.00	-4.83	-1.42
SD	10.41	14.34	12.47
Median	3.00	-4.50	-1.00
Min : Max	-14.00 : 15.00	-30.00 : 10.00	-30.00 : 15.00

Table 17 : Clinical parameters - Intervention period - Diuresis - Changes vs Day-0 visit - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	6	12
Mean	1.63	1.62	1.62
SD	0.63	0.68	0.63
Median	1.43	1.93	1.68
Min : Max	1.10 : 2.70	0.55 : 2.20	0.55 : 2.70
Day-14 visit			
no. pts.	6	6	12
Mean	1.78	1.78	1.78
SD	0.47	0.68	0.56
Median	1.75	1.90	1.90
Min : Max	1.20 : 2.50	0.60 : 2.50	0.60 : 2.50
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.16	0.17	0.16
SD	0.24	0.21	0.22
Median	0.17	0.12	0.15
Min : Max	-0.20 : 0.40	-0.10 : 0.50	-0.20 : 0.50
Day-28 visit			
no. pts.	6	6	12
Mean	1.58	1.70	1.64
SD	0.48	0.66	0.56
Median	1.50	1.80	1.70
Min : Max	1.10 : 2.30	0.50 : 2.50	0.50 : 2.50
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.04	0.08	0.02
SD	0.39	0.32	0.35
Median	-0.05	0.00	-0.03
Min : Max	-0.70 : 0.40	-0.30 : 0.60	-0.70 : 0.60

Table 18 : Clinical parameters - Intervention period - Hyperhydratation signs - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
No	6(100.0%)	6(100.0%)	12(100.0%)
Day-14 visit			
No	6(100.0%)	6(100.0%)	12 (92.3%)
Day-28 visit			
Yes		1 (16.7%)	1 (8.3%)
No	6(100.0%)	5 (83.3%)	11 (91.7%)

Table 19 : Functional parameters – Weekly total urea Kt/V - Changes vs Day-0 visit - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	6	12
Mean	1.35	1.27	1.31
SD	0.23	0.29	0.25
Median	1.34	1.30	1.30
Min : Max	1.10 : 1.68	0.76 : 1.59	0.76 : 1.68
Day-28 visit			
no. pts.	6	6	12
Mean	1.38	1.45	1.41
SD	0.26	0.22	0.23
Median	1.42	1.50	1.44
Min : Max	1.07 : 1.70	1.12 : 1.75	1.07 : 1.75
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.03	0.18	0.11
SD	0.15	0.30	0.24
Median	0.01	0.10	0.07
Min : Max	-0.16 : 0.30	-0.11 : 0.76	-0.16 : 0.76

Table 20 : Functional parameters – Peritoneal equilibration test (PET) - Dialysate/Plasma creatinine - Changes vs Day-0 visit
- Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	6	12
Mean	0.51	0.64	0.57
SD	0.15	0.07	0.13
Median	0.57	0.64	0.60
Min : Max	0.22 : 0.62	0.53 : 0.71	0.22 : 0.71
Day-28 visit			
no. pts.	6	6	12
Mean	0.64	0.65	0.64
SD	0.05	0.07	0.06
Median	0.62	0.66	0.64
Min : Max	0.59 : 0.72	0.56 : 0.74	0.56 : 0.74
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.12	0.02	0.07
SD	0.19	0.07	0.15
Median	0.04	0.04	0.04
Min : Max	0.01 : 0.50	-0.12 : 0.08	-0.12 : 0.50

Table 21 : Functional parameters – Weekly total creatinine clearance - Dialysate/Plasma creatinine - Changes vs Day-0 visit
- Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	6	12
Mean	73.37	63.40	68.38
SD	17.06	15.05	16.20
Median	77.90	62.04	67.42
Min : Max	50.03 : 93.39	43.28 : 86.94	43.28 : 93.39
Day-28 visit			
no. pts.	6	6	12
Mean	76.53	65.66	71.09
SD	23.91	18.93	21.33
Median	79.90	65.70	67.85
Min : Max	42.38 : 105.74	42.69 : 98.15	42.38 : 105.74
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	3.16	2.26	2.71
SD	16.64	6.63	12.09
Median	6.03	1.18	2.36
Min : Max	-22.59 : 24.79	-6.39 : 11.21	-22.59 : 24.79

Table 22 : Ultrafiltration - Total ultrafiltration (mL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	6	12
Mean	158.33	550.00	354.17
SD	142.89	467.97	388.15
Median	175.00	400.00	300.00
Min : Max	0.00 : 300.00	300.00 : 1500.0	0.00 : 1500.0
Day-14 visit			
no. pts.	6	6	12
Mean	208.33	508.33	358.33
SD	91.74	307.27	267.00
Median	225.00	350.00	300.00
Min : Max	100.00 : 300.00	300.00 : 1050.0	100.00 : 1050.0
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	50.00	-41.67	4.17
SD	89.44	241.70	180.23
Median	75.00	0.00	0.00
Min : Max	-100.0 : 150.00	-450.0 : 300.00	-450.0 : 300.00
Day-28 visit			
no. pts.	6	6	12
Mean	200.00	508.33	354.17
SD	89.44	297.35	264.11
Median	200.00	350.00	300.00
Min : Max	100.00 : 300.00	300.00 : 1000.0	100.00 : 1000.0
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	41.67	-41.67	0.00
SD	102.06	272.79	201.13
Median	25.00	0.00	0.00
Min : Max	-100.0 : 200.00	-500.0 : 350.00	-500.0 : 350.00

Table 23 : Ultrafiltration - CA 125 (U.a./mL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	5	11
Mean	78.02	44.52	62.79
SD	53.68	30.27	45.97
Median	57.00	45.50	52.60
Min : Max	42.90 : 184.00	9.90 : 88.60	9.90 : 184.00
Day-14 visit			
no. pts.	6	6	12
Mean	81.40	43.58	62.49
SD	60.15	20.73	47.22
Median	59.85	51.85	54.35
Min : Max	45.30 : 203.10	10.90 : 62.00	10.90 : 203.10
Day-14 - Changes vs Day-0			
no. pts.	6	5	11
Mean	3.38	-2.58	0.67
SD	12.18	19.84	15.54
Median	4.00	1.10	1.90
Min : Max	-13.00 : 19.10	-36.70 : 14.30	-36.70 : 19.10
Day-28 visit			
no. pts.	6	6	12
Mean	95.48	71.58	83.53
SD	56.85	51.01	52.99
Median	71.65	70.20	70.80
Min : Max	60.90 : 209.20	11.90 : 145.90	11.90 : 209.20
Day-28 - Changes vs Day-0			
no. pts.	6	5	11
Mean	17.47	26.64	21.64
SD	17.06	37.68	27.13
Median	19.95	20.80	20.80
Min : Max	-13.10 : 32.50	-2.10 : 91.30	-13.10 : 91.30

Table 24 : Ultrafiltration - Proteins (mg/L) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	4	10
Mean	0.80	1.03	0.89
SD	0.00	0.82	0.49
Median	0.80	0.80	0.80
Min : Max	0.80 : 0.80	0.30 : 2.20	0.30 : 2.20
Day-14 visit			
no. pts.	6	5	11
Mean	0.80	0.82	0.81
SD	0.00	0.84	0.53
Median	0.80	0.80	0.80
Min : Max	0.80 : 0.80	0.00 : 2.20	0.00 : 2.20
Day-14 - Changes vs Day-0			
no. pts.	6	4	10
Mean	0.00	0.00	0.00
SD	0.00	0.00	0.00
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00
Day-28 visit			
no. pts.	6	6	12
Mean	0.80	1.02	0.91
SD	0.00	0.80	0.55
Median	0.80	0.80	0.80
Min : Max	0.80 : 0.80	0.30 : 2.60	0.30 : 2.60
Day-28 - Changes vs Day-0			
no. pts.	6	5	11
Mean	0.00	0.18	0.08
SD	0.00	1.33	0.85
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	-1.40 : 2.30	-1.40 : 2.30

Table 25 : Uric acid (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	6	6	12
Mean	5.88	5.15	5.52
SD	2.14	1.95	1.99
Median	5.20	4.65	4.70
Min : Max	4.30 : 9.90	3.30 : 8.90	3.30 : 9.90
Day-14 visit			
no. pts.	6	6	12
Mean	5.23	5.58	5.41
SD	1.26	2.53	1.91
Median	4.75	5.15	4.75
Min : Max	4.20 : 7.50	2.70 : 9.70	2.70 : 9.70
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.65	0.43	-0.11
SD	2.24	1.93	2.07
Median	-0.05	0.45	0.15
Min : Max	-5.10 : 1.20	-1.70 : 3.80	-5.10 : 3.80
Day-28 visit			
no. pts.	6	6	12
Mean	5.42	5.63	5.53
SD	1.24	1.72	1.43
Median	5.25	5.35	5.35
Min : Max	4.10 : 6.90	3.50 : 7.70	3.50 : 7.70
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.47	0.48	0.01
SD	1.27	2.11	1.73
Median	-0.05	0.25	0.05
Min : Max	-3.00 : 0.40	-1.40 : 4.40	-3.00 : 4.40

Table 26 : Lactic acid (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Day-0 visit			
no. pts.	5	6	11
Mean	11.60	6.63	8.89
SD	5.46	5.73	5.92
Median	10.00	6.00	9.00
Min : Max	7.00 : 21.00	0.70 : 15.30	0.70 : 21.00
Day-14 visit			
no. pts.	5	6	11
Mean	11.60	7.64	9.44
SD	5.92	6.23	6.14
Median	9.90	7.45	9.90
Min : Max	5.00 : 19.80	0.90 : 14.95	0.90 : 19.80
Day-14 - Changes vs Day-0			
no. pts.	5	6	11
Mean	0.00	1.01	0.55
SD	3.68	1.97	2.76
Median	-1.20	0.25	-0.10
Min : Max	-3.00 : 6.30	-1.00 : 3.90	-3.00 : 6.30
Day-28 visit			
no. pts.	6	5	11
Mean	10.22	9.12	9.72
SD	2.70	5.92	4.24
Median	10.50	9.00	10.00
Min : Max	7.00 : 13.50	0.60 : 17.11	0.60 : 17.11
Day-28 - Changes vs Day-0			
no. pts.	6	5	11
Mean	-0.65	1.30	0.24
SD	3.70	5.31	4.38
Median	0.50	3.00	1.00
Min : Max	-7.50 : 2.80	-7.20 : 6.11	-7.50 : 6.11

Table 27.1 : Adverse events

	Group A No. pts (%) (n=7)	Group B No. pts (%) (n=6)	All No. pts (%) (n=13)
Total no. of events	1	8	9
No. of patients with event	1 (14.3%)	4 (66.7%)	5 (38.5%)

Table 27.2 : Adverse events – details

Treatment group	Patient no.	AE no.	Adverse ewvent	Intensity	Relationship with study drug	Action taken: None	Action taken: Study drug interrupted and restarted	Action taken: Dose reduced	Action taken: Study drug Discontinued	Action taken: Specific therapy/ medication	Action taken: Hospitalization	Outcome
Group A	01-004	1	Hyperphosphataemia	Mild	Not related	Yes	.	.	.	.	.	Not recovered
Group B	01-002	1	Turbid peritoneal fluid	Mild	Not related	Yes	.	.	.	.	.	Not recovered
	01-003	1	Anemia	Mild	Not related	No	No	No	No	Yes	No	Not recovered
	05-001	1	Macroglossia	Mild	Unlikely related	Yes	.	.	.	.	.	Not recovered
		2	insomnia	Mild	Not related	Yes	.	.	.	.	.	Not recovered
		3	Dispnea	Mild	Unlikely related	No	No	No	No	Yes	No	Not recovered
	05-002	1	itching	Mild	Not related	Yes	.	.	.	.	.	Not recovered
		2	swollen legs	Mild	Unlikely related	Yes	.	.	.	.	.	Not recovered
		3	mild bilateral legs edema	Mild	Unlikely related	Yes	.	.	.	.	.	Not recovered

Table 28.1 : ECG test at day-0 and day-28 visits - - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
ECG normal ?			
Day-0 visit			
Yes	2 (33.3%)	5 (83.3%)	7 (58.3%)
No	4 (66.7%)	1 (16.6%)	5 (41.7%)
Day-28 visit			
Yes	4 (66.7%)	5 (83.3%)	9 (75.0%)
No	2 (33.3%)	1 (16.7%)	3 (25.0%)

Table 28.2 : ECG test - changes details

Treatment group	Patient no.	visit_label	ECG test abnormality	Clinical evaluation
Group A	01-005	Screening Period: Day 0	Sinus Bradycardia	Not Clinically Significant
	01-006	Screening Period: Day 0	Sinus Bradycardia	Not Clinically Significant
	01-006	Intervention Period: Day 28	Right Bundle Branch Block	Not Clinically Significant
	01-007	Screening Period: Day 0	Left Bundle Branch Block	Not Clinically Significant
	01-007	Intervention Period: Day 28	Left Bundle Branch Block	Not Clinically Significant
	01-009	Screening Period: Day 0	Sinus rhythm, previous lower myocardial infarction	Not Clinically Significant
Group B	01-001	Screening Period: Day 0	Sinus Bradycardia	Not Clinically Significant
	01-001	Intervention Period: Day 28	Sinus Bradycardia	Clinically significant for concomitant disease

Table 29.1: Hematology - RBC count (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	7	6	13
Mean	3.76	3.88	3.82
SD	0.48	0.46	0.45
Median	3.71	3.99	3.91
Min : Max	3.07 : 4.48	3.03 : 4.31	3.03 : 4.48
Day-14 visit			
no. pts.	6	6	12
Mean	3.73	3.92	3.83
SD	0.35	0.52	0.43
Median	3.71	3.98	3.89
Min : Max	3.22 : 4.13	3.03 : 4.64	3.03 : 4.64
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.04	0.04	0.00
SD	0.31	0.17	0.24
Median	0.10	0.03	0.06
Min : Max	-0.49 : 0.21	-0.14 : 0.33	-0.49 : 0.33
Day-28 visit			
no. pts.	6	6	12
Mean	3.77	3.64	3.71
SD	0.24	0.53	0.40
Median	3.70	3.59	3.70
Min : Max	3.51 : 4.15	2.92 : 4.28	2.92 : 4.28
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.00	-0.23	-0.12
SD	0.47	0.30	0.40
Median	0.11	-0.15	-0.12
Min : Max	-0.59 : 0.66	-0.77 : 0.11	-0.77 : 0.66

Table 29.2: Hematology - Hematocrit (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	7	6	13
Mean	34.57	35.23	34.88
SD	4.38	4.32	4.18
Median	35.10	35.85	35.60
Min : Max	27.60 : 42.00	26.90 : 39.10	26.90 : 42.00
Day-14 visit			
no. pts.	6	6	12
Mean	33.92	35.40	34.66
SD	2.94	4.62	3.77
Median	33.50	36.45	36.20
Min : Max	29.60 : 37.40	26.50 : 40.20	26.50 : 40.20
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.42	0.17	-0.13
SD	2.78	0.89	1.99
Median	0.65	0.40	0.40
Min : Max	-4.60 : 2.00	-1.30 : 1.10	-4.60 : 2.00
Day-28 visit			
no. pts.	6	6	12
Mean	33.97	32.67	33.32
SD	2.04	4.86	3.62
Median	33.65	32.85	33.65
Min : Max	30.80 : 36.90	25.80 : 39.50	25.80 : 39.50
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.37	-2.57	-1.47
SD	4.67	2.77	3.83
Median	0.75	-2.50	-1.40
Min : Max	-6.70 : 5.90	-6.70 : 1.40	-6.70 : 5.90

Table 29.3: Hematology - Hemoglobin (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	7	6	13
Mean	11.04	11.22	11.12
SD	1.43	1.18	1.27
Median	11.30	11.55	11.50
Min : Max	8.50 : 13.20	8.90 : 12.20	8.50 : 13.20
Day-14 visit			
no. pts.	6	6	12
Mean	10.95	11.30	11.13
SD	1.21	1.33	1.23
Median	10.90	11.55	11.35
Min : Max	9.00 : 12.20	8.80 : 12.70	8.80 : 12.70
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.05	0.08	0.02
SD	0.81	0.40	0.61
Median	0.25	0.10	0.15
Min : Max	-1.10 : 0.70	-0.40 : 0.50	-1.10 : 0.70
Day-28 visit			
no. pts.	6	6	12
Mean	11.02	10.60	10.81
SD	0.78	1.45	1.13
Median	10.90	10.70	10.90
Min : Max	10.10 : 12.20	8.60 : 12.30	8.60 : 12.30
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.02	-0.62	-0.30
SD	1.35	0.93	1.15
Median	0.35	-0.30	-0.30
Min : Max	-1.60 : 1.90	-2.20 : 0.50	-2.20 : 1.90

Table 29.4: Hematology - WBC count (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	7	6	13
Mean	7.25	11.49	9.21
SD	3.47	9.93	7.21
Median	6.01	8.23	6.52
Min : Max	4.28 : 14.27	4.19 : 31.21	4.19 : 31.21
Day-14 visit			
no. pts.	6	6	12
Mean	6.89	12.19	9.54
SD	2.21	11.65	8.46
Median	6.77	8.13	7.90
Min : Max	4.58 : 10.12	5.97 : 35.84	4.58 : 35.84
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.86	0.70	-0.08
SD	1.97	2.65	2.37
Median	-0.69	0.74	-0.20
Min : Max	-4.15 : 1.80	-2.16 : 4.63	-4.15 : 4.63
Day-28 visit			
no. pts.	6	6	12
Mean	7.18	11.92	9.55
SD	2.19	11.76	8.44
Median	7.04	7.28	7.28
Min : Max	4.90 : 10.61	5.27 : 35.75	4.90 : 35.75
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.56	0.43	-0.07
SD	1.82	2.88	2.35
Median	-0.30	0.76	0.20
Min : Max	-3.66 : 1.77	-4.31 : 4.54	-4.31 : 4.54

Table 29.5: Hematology - Neutrophils (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	7	6	13
Mean	5.16	4.88	5.03
SD	3.04	2.26	2.60
Median	4.42	4.54	4.42
Min : Max	2.52 : 11.35	2.10 : 8.67	2.10 : 11.35
Day-14 visit			
no. pts.	6	6	12
Mean	4.88	4.61	4.75
SD	1.92	0.90	1.44
Median	4.68	4.38	4.38
Min : Max	2.72 : 7.63	3.71 : 6.29	2.72 : 7.63
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.64	-0.27	-0.46
SD	1.71	1.51	1.55
Median	-0.40	-0.08	-0.40
Min : Max	-3.72 : 1.41	-2.38 : 1.62	-3.72 : 1.62
Day-28 visit			
no. pts.	6	6	12
Mean	5.11	5.46	5.29
SD	1.97	1.89	1.85
Median	4.90	4.96	4.96
Min : Max	2.93 : 8.11	3.23 : 7.77	2.93 : 8.11
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.41	0.58	0.08
SD	1.67	2.61	2.15
Median	-0.29	0.61	0.13
Min : Max	-3.24 : 1.74	-3.71 : 4.18	-3.71 : 4.18

Table 29.6: Hematology - Basophils (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	7	6	13
Mean	0.05	0.05	0.05
SD	0.02	0.03	0.02
Median	0.04	0.04	0.04
Min : Max	0.01 : 0.07	0.01 : 0.09	0.01 : 0.09
Day-14 visit			
no. pts.	6	6	12
Mean	0.05	0.05	0.05
SD	0.02	0.03	0.03
Median	0.06	0.04	0.06
Min : Max	0.03 : 0.07	0.01 : 0.10	0.01 : 0.10
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.00	0.00	-0.00
SD	0.02	0.03	0.02
Median	0.00	0.01	0.00
Min : Max	-0.03 : 0.02	-0.03 : 0.03	-0.03 : 0.03
Day-28 visit			
no. pts.	6	6	12
Mean	0.05	0.05	0.05
SD	0.02	0.04	0.03
Median	0.06	0.04	0.06
Min : Max	0.02 : 0.07	0.02 : 0.10	0.02 : 0.10
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.00	0.01	0.00
SD	0.01	0.02	0.02
Median	0.00	0.01	0.00
Min : Max	-0.02 : 0.02	-0.02 : 0.03	-0.02 : 0.03

Table 29.7: Hematology - Eosinophils (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	7	6	13
Mean	0.33	0.15	0.25
SD	0.19	0.11	0.18
Median	0.26	0.18	0.19
Min : Max	0.14 : 0.65	0.00 : 0.31	0.00 : 0.65
Day-14 visit			
no. pts.	6	6	12
Mean	0.25	0.19	0.22
SD	0.13	0.11	0.12
Median	0.23	0.20	0.21
Min : Max	0.10 : 0.43	0.00 : 0.34	0.00 : 0.43
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.10	0.04	-0.03
SD	0.09	0.08	0.11
Median	-0.10	0.02	-0.02
Min : Max	-0.22 : 0.01	-0.07 : 0.16	-0.22 : 0.16
Day-28 visit			
no. pts.	6	6	12
Mean	0.25	0.17	0.21
SD	0.13	0.11	0.12
Median	0.25	0.20	0.22
Min : Max	0.09 : 0.48	0.00 : 0.30	0.00 : 0.48
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.09	0.02	-0.04
SD	0.12	0.07	0.11
Median	-0.06	0.02	0.00
Min : Max	-0.29 : 0.03	-0.08 : 0.12	-0.29 : 0.12

Table 29.8: Hematology - Lymphocytes (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	7	6	13
Mean	1.09	5.76	3.24
SD	0.25	10.28	7.07
Median	1.18	1.52	1.27
Min : Max	0.69 : 1.38	1.24 : 26.73	0.69 : 26.73
Day-14 visit			
no. pts.	6	6	12
Mean	1.12	6.57	3.84
SD	0.26	11.58	8.31
Median	1.15	1.92	1.38
Min : Max	0.68 : 1.40	1.36 : 30.19	0.68 : 30.19
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.04	0.81	0.39
SD	0.21	1.36	1.03
Median	-0.10	0.33	0.15
Min : Max	-0.23 : 0.34	-0.39 : 3.46	-0.39 : 3.46
Day-28 visit			
no. pts.	6	6	12
Mean	1.15	5.60	3.38
SD	0.11	10.41	7.39
Median	1.19	1.39	1.21
Min : Max	0.96 : 1.25	1.02 : 26.84	0.96 : 26.84
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.00	-0.16	-0.08
SD	0.12	0.33	0.25
Median	-0.03	-0.09	-0.03
Min : Max	-0.15 : 0.14	-0.60 : 0.20	-0.60 : 0.20

Table 29.9: Hematology - Monocytes (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	7	6	13
Mean	0.62	0.65	0.64
SD	0.23	0.18	0.20
Median	0.57	0.64	0.57
Min : Max	0.30 : 1.02	0.48 : 0.88	0.30 : 1.02
Day-14 visit			
no. pts.	6	6	12
Mean	0.59	0.77	0.68
SD	0.16	0.29	0.24
Median	0.58	0.72	0.64
Min : Max	0.43 : 0.86	0.43 : 1.28	0.43 : 1.28
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.08	0.12	0.02
SD	0.19	0.37	0.30
Median	-0.06	0.01	-0.04
Min : Max	-0.38 : 0.20	-0.22 : 0.77	-0.38 : 0.77
Day-28 visit			
no. pts.	6	6	12
Mean	0.62	0.63	0.62
SD	0.13	0.16	0.14
Median	0.58	0.58	0.58
Min : Max	0.49 : 0.85	0.49 : 0.84	0.49 : 0.85
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.06	-0.02	-0.04
SD	0.16	0.27	0.21
Median	-0.05	0.04	-0.02
Min : Max	-0.27 : 0.20	-0.38 : 0.33	-0.38 : 0.33

Table 29.10: Hematology - Platelets count (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	7	6	13
Mean	224.43	225.50	224.92
SD	63.82	77.98	67.60
Median	225.00	225.00	225.00
Min : Max	117.00 : 301.00	132.00 : 349.00	117.00 : 349.00
Day-14 visit			
no. pts.	6	6	12
Mean	249.83	238.17	244.00
SD	53.82	97.02	75.05
Median	225.00	242.50	225.00
Min : Max	205.00 : 342.00	122.00 : 333.00	122.00 : 342.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	7.50	12.67	10.08
SD	18.96	49.27	35.69
Median	-0.50	0.50	-0.50
Min : Max	-11.00 : 41.00	-47.00 : 73.00	-47.00 : 73.00
Day-28 visit			
no. pts.	6	6	12
Mean	261.67	229.00	245.33
SD	46.19	65.97	56.91
Median	240.50	232.00	238.50
Min : Max	226.00 : 344.00	134.00 : 305.00	134.00 : 344.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	19.33	3.50	11.42
SD	45.61	56.68	49.74
Median	30.50	16.00	20.50
Min : Max	-68.00 : 62.00	-106.0 : 51.00	-106.0 : 62.00

Table 30.1: Biochemistry - BUN (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	149.20	168.45	158.83
SD	46.95	48.12	46.43
Median	163.50	173.00	167.00
Min : Max	74.20 : 202.00	79.70 : 219.00	74.20 : 219.00
Day-14 visit			
no. pts.	6	6	12
Mean	174.00	152.45	163.23
SD	43.24	70.99	57.16
Median	180.00	130.50	154.00
Min : Max	119.00 : 225.00	82.10 : 260.00	82.10 : 260.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	24.80	-16.00	4.40
SD	41.67	62.90	55.15
Median	25.50	-10.00	11.20
Min : Max	-45.00 : 84.80	-104.4 : 83.00	-104.4 : 84.80
Day-28 visit			
no. pts.	6	6	12
Mean	152.62	146.28	149.45
SD	59.32	68.13	61.00
Median	140.50	140.47	140.50
Min : Max	87.74 : 245.00	81.20 : 246.00	81.20 : 246.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	3.42	-22.17	-9.37
SD	32.91	64.67	50.71
Median	6.27	-15.75	0.25
Min : Max	-51.00 : 43.00	-102.1 : 69.00	-102.1 : 69.00

Table 30.2: Biochemistry - Creatinine (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	7.60	9.04	8.32
SD	1.89	2.19	2.09
Median	7.68	8.12	8.12
Min : Max	5.64 : 9.96	6.97 : 12.83	5.64 : 12.83
Day-14 visit			
no. pts.	6	6	12
Mean	7.32	9.68	8.50
SD	1.45	2.47	2.29
Median	7.11	8.79	8.14
Min : Max	5.65 : 9.31	7.62 : 14.12	5.65 : 14.12
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.28	0.65	0.18
SD	1.08	0.52	0.94
Median	0.04	0.69	0.40
Min : Max	-2.38 : 0.49	-0.14 : 1.29	-2.38 : 1.29
Day-28 visit			
no. pts.	6	6	12
Mean	7.46	9.24	8.35
SD	1.76	2.06	2.05
Median	7.17	8.85	8.39
Min : Max	5.42 : 10.00	7.23 : 12.71	5.42 : 12.71
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.15	0.21	0.03
SD	1.00	0.47	0.77
Median	-0.15	0.13	-0.04
Min : Max	-1.92 : 1.00	-0.37 : 0.89	-1.92 : 1.00

Table 30.3: Biochemistry - Glucose (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	108.17	114.50	111.33
SD	31.48	26.64	28.00
Median	110.50	116.00	111.00
Min : Max	71.00 : 148.00	87.00 : 141.00	71.00 : 148.00
Day-14 visit			
no. pts.	6	6	12
Mean	93.33	104.33	98.83
SD	13.38	21.86	18.21
Median	96.50	95.50	96.50
Min : Max	73.00 : 112.00	82.00 : 136.00	73.00 : 136.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-14.83	-10.17	-12.50
SD	22.89	20.95	21.06
Median	-8.50	-3.50	-3.50
Min : Max	-50.00 : 6.00	-51.00 : 9.00	-51.00 : 9.00
Day-28 visit			
no. pts.	6	6	12
Mean	115.33	140.00	127.67
SD	27.35	50.30	40.69
Median	110.50	123.00	114.00
Min : Max	83.00 : 166.00	92.00 : 222.00	83.00 : 222.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	7.17	25.50	16.33
SD	30.75	36.59	33.61
Median	9.50	21.50	10.00
Min : Max	-41.00 : 42.00	-19.00 : 84.00	-41.00 : 84.00

Table 30.4: Biochemistry - Total Cholesterol (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	171.67	137.83	154.75
SD	18.42	15.01	23.85
Median	173.00	138.00	152.50
Min : Max	143.00 : 196.00	113.00 : 156.00	113.00 : 196.00
Day-14 visit			
no. pts.	6	6	12
Mean	181.33	138.00	159.67
SD	29.74	21.32	33.48
Median	188.50	136.00	148.50
Min : Max	145.00 : 220.00	113.00 : 172.00	113.00 : 220.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	9.67	0.17	4.92
SD	21.24	15.59	18.44
Median	11.50	4.00	5.50
Min : Max	-21.00 : 38.00	-29.00 : 16.00	-29.00 : 38.00
Day-28 visit			
no. pts.	6	6	12
Mean	176.00	133.83	154.92
SD	40.79	17.55	37.17
Median	170.00	134.00	141.50
Min : Max	136.00 : 245.00	109.00 : 161.00	109.00 : 245.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	4.33	-4.00	0.17
SD	42.30	16.60	30.94
Median	-5.50	2.50	-1.00
Min : Max	-44.00 : 82.00	-33.00 : 10.00	-44.00 : 82.00

Table 30.5: Biochemistry - HDL Cholesterol (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	37.17	47.00	42.08
SD	11.41	17.56	15.02
Median	34.50	45.50	40.50
Min : Max	25.00 : 52.00	25.00 : 78.00	25.00 : 78.00
Day-14 visit			
no. pts.	6	6	12
Mean	36.17	42.83	39.50
SD	7.86	10.21	9.36
Median	35.00	42.00	38.00
Min : Max	28.00 : 50.00	29.00 : 54.00	28.00 : 54.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-1.00	-4.17	-2.58
SD	6.48	10.57	8.52
Median	-0.50	-2.00	-1.50
Min : Max	-12.00 : 7.00	-24.00 : 5.00	-24.00 : 7.00
Day-28 visit			
no. pts.	6	6	12
Mean	36.83	43.17	40.00
SD	10.74	6.71	9.16
Median	34.00	46.00	40.50
Min : Max	27.00 : 56.00	31.00 : 49.00	27.00 : 56.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.33	-3.83	-2.08
SD	5.68	13.59	10.09
Median	1.00	0.50	0.50
Min : Max	-9.00 : 6.00	-31.00 : 6.00	-31.00 : 6.00

Table 30.6: Biochemistry - LDL Cholesterol (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	96.83	65.83	81.33
SD	15.28	11.51	20.70
Median	100.50	72.00	74.00
Min : Max	70.00 : 114.00	47.00 : 75.00	47.00 : 114.00
Day-14 visit			
no. pts.	6	6	12
Mean	90.83	65.67	78.25
SD	22.99	14.45	22.54
Median	87.00	70.50	72.00
Min : Max	67.00 : 117.00	37.00 : 77.00	37.00 : 117.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-6.00	-0.17	-3.08
SD	13.43	7.28	10.74
Median	-5.00	-2.00	-3.00
Min : Max	-21.00 : 13.00	-10.00 : 11.00	-21.00 : 13.00
Day-28 visit			
no. pts.	6	6	12
Mean	93.67	65.00	79.33
SD	25.13	12.21	24.06
Median	91.00	68.50	72.50
Min : Max	63.00 : 133.00	43.00 : 79.00	43.00 : 133.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-3.17	-0.83	-2.00
SD	16.96	4.26	11.86
Median	-6.50	-2.50	-4.50
Min : Max	-22.00 : 29.00	-5.00 : 5.00	-22.00 : 29.00

Table 30.7: Biochemistry - Triglycerides (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	183.00	128.67	155.83
SD	107.80	48.25	84.53
Median	141.00	122.50	137.50
Min : Max	85.00 : 364.00	77.00 : 189.00	77.00 : 364.00
Day-14 visit			
no. pts.	6	5	11
Mean	292.33	149.80	227.55
SD	261.60	77.23	205.29
Median	178.00	112.00	169.00
Min : Max	130.00 : 808.00	66.00 : 244.00	66.00 : 808.00
Day-14 - Changes vs Day-0			
no. pts.	6	5	11
Mean	109.33	24.20	70.64
SD	164.18	28.63	125.62
Median	41.50	24.00	36.00
Min : Max	35.00 : 444.00	-11.00 : 67.00	-11.00 : 444.00
Day-28 visit			
no. pts.	5	6	11
Mean	198.00	132.00	162.00
SD	99.89	52.55	81.00
Median	154.00	101.00	128.00
Min : Max	107.00 : 344.00	97.00 : 217.00	97.00 : 344.00
Day-28 - Changes vs Day-0			
no. pts.	5	6	11
Mean	4.60	3.33	3.91
SD	23.29	28.17	24.78
Median	1.00	6.00	1.00
Min : Max	-20.00 : 43.00	-42.00 : 40.00	-42.00 : 43.00

Table 30.8: Biochemistry - Total proteins (g/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	6.53	6.10	6.32
SD	0.56	0.51	0.56
Median	6.60	6.10	6.40
Min : Max	5.90 : 7.30	5.50 : 6.70	5.50 : 7.30
Day-14 visit			
no. pts.	6	6	12
Mean	6.60	6.20	6.40
SD	0.42	0.53	0.50
Median	6.55	6.15	6.50
Min : Max	6.10 : 7.30	5.60 : 6.90	5.60 : 7.30
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.07	0.10	0.08
SD	0.23	0.17	0.19
Median	0.05	0.15	0.10
Min : Max	-0.30 : 0.40	-0.10 : 0.30	-0.30 : 0.40
Day-28 visit			
no. pts.	6	6	12
Mean	6.55	6.02	6.28
SD	0.34	0.48	0.49
Median	6.65	6.00	6.50
Min : Max	5.90 : 6.90	5.40 : 6.60	5.40 : 6.90
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.02	-0.08	-0.03
SD	0.35	0.19	0.27
Median	-0.05	-0.10	-0.10
Min : Max	-0.40 : 0.60	-0.40 : 0.20	-0.40 : 0.60

Table 30.9: Biochemistry - Albumin (g/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	3.73	3.36	3.55
SD	0.18	0.73	0.54
Median	3.65	3.55	3.60
Min : Max	3.60 : 4.00	2.00 : 4.10	2.00 : 4.10
Day-14 visit			
no. pts.	6	6	12
Mean	3.80	3.57	3.68
SD	0.11	0.60	0.43
Median	3.80	3.75	3.80
Min : Max	3.70 : 4.00	2.40 : 4.10	2.40 : 4.10
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.07	0.21	0.14
SD	0.15	0.17	0.17
Median	0.10	0.20	0.15
Min : Max	-0.20 : 0.20	0.00 : 0.40	-0.20 : 0.40
Day-28 visit			
no. pts.	6	6	12
Mean	3.24	3.48	3.36
SD	1.47	0.68	1.10
Median	3.75	3.60	3.70
Min : Max	0.25 : 4.00	2.20 : 4.10	0.25 : 4.10
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.49	0.13	-0.18
SD	1.42	0.11	1.01
Median	0.00	0.15	0.05
Min : Max	-3.35 : 0.40	0.00 : 0.26	-3.35 : 0.40

Table 30.10: Biochemistry - Total bilirubin (mg/dL) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	0.46	0.56	0.51
SD	0.11	0.23	0.18
Median	0.44	0.55	0.50
Min : Max	0.35 : 0.61	0.30 : 0.86	0.30 : 0.86
Day-14 visit			
no. pts.	6	6	12
Mean	0.53	0.54	0.54
SD	0.13	0.21	0.17
Median	0.51	0.56	0.51
Min : Max	0.37 : 0.71	0.30 : 0.77	0.30 : 0.77
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.08	-0.01	0.03
SD	0.09	0.04	0.08
Median	0.07	0.00	0.00
Min : Max	-0.03 : 0.21	-0.09 : 0.02	-0.09 : 0.21
Day-28 visit			
no. pts.	6	5	11
Mean	0.39	0.50	0.44
SD	0.13	0.26	0.20
Median	0.34	0.49	0.35
Min : Max	0.25 : 0.57	0.20 : 0.82	0.20 : 0.82
Day-28 - Changes vs Day-0			
no. pts.	6	5	11
Mean	-0.07	0.01	-0.03
SD	0.06	0.13	0.10
Median	-0.08	-0.01	-0.07
Min : Max	-0.15 : 0.02	-0.10 : 0.22	-0.15 : 0.22

Table 30.11: Biochemistry - SGOT (AST) (U/L) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	11.83	14.50	13.17
SD	3.31	4.28	3.90
Median	12.00	14.50	14.00
Min : Max	7.00 : 15.00	8.00 : 20.00	7.00 : 20.00
Day-14 visit			
no. pts.	6	6	12
Mean	13.50	15.67	14.58
SD	2.95	3.78	3.42
Median	13.00	16.00	14.50
Min : Max	11.00 : 19.00	9.00 : 20.00	9.00 : 20.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	1.67	1.17	1.42
SD	4.23	1.47	3.03
Median	0.50	0.50	0.50
Min : Max	-2.00 : 9.00	0.00 : 3.00	-2.00 : 9.00
Day-28 visit			
no. pts.	6	6	12
Mean	13.33	14.50	13.92
SD	5.13	4.76	4.76
Median	12.50	15.00	14.50
Min : Max	8.00 : 22.00	7.00 : 21.00	7.00 : 22.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	1.50	0.00	0.75
SD	5.61	4.00	4.71
Median	0.50	1.00	0.50
Min : Max	-5.00 : 12.00	-6.00 : 4.00	-6.00 : 12.00

Table 30.12: Biochemistry - SGPT (ALT) (U/L) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	12.67	16.17	14.42
SD	2.73	6.31	4.98
Median	12.50	16.00	13.50
Min : Max	9.00 : 17.00	9.00 : 27.00	9.00 : 27.00
Day-14 visit			
no. pts.	6	6	12
Mean	15.67	25.50	20.58
SD	7.17	16.55	13.20
Median	15.00	20.50	17.50
Min : Max	8.00 : 28.00	9.00 : 54.00	8.00 : 54.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	3.00	9.33	6.17
SD	6.00	13.41	10.44
Median	0.00	5.00	2.50
Min : Max	-1.00 : 14.00	0.00 : 36.00	-1.00 : 36.00
Day-28 visit			
no. pts.	6	6	12
Mean	16.50	19.67	18.08
SD	12.05	10.61	10.95
Median	11.50	16.50	14.00
Min : Max	7.00 : 40.00	7.00 : 34.00	7.00 : 40.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	3.83	3.50	3.67
SD	11.43	6.44	8.85
Median	0.00	3.00	0.00
Min : Max	-6.00 : 26.00	-3.00 : 13.00	-6.00 : 26.00

Table 30.13: Biochemistry - Alkaline Phosphatase (U/L) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	66.17	107.33	86.75
SD	15.79	40.59	36.39
Median	61.50	98.00	74.50
Min : Max	53.00 : 94.00	64.00 : 167.00	53.00 : 167.00
Day-14 visit			
no. pts.	5	5	10
Mean	60.80	110.40	85.60
SD	17.08	32.86	35.96
Median	63.00	111.00	79.00
Min : Max	38.00 : 85.00	73.00 : 161.00	38.00 : 161.00
Day-14 - Changes vs Day-0			
no. pts.	5	5	10
Mean	-7.40	15.00	3.80
SD	6.35	28.13	22.56
Median	-9.00	10.00	-1.50
Min : Max	-16.00 : 1.00	-26.00 : 47.00	-26.00 : 47.00
Day-28 visit			
no. pts.	5	6	11
Mean	64.60	120.17	94.91
SD	17.42	42.85	43.37
Median	64.00	117.00	86.00
Min : Max	43.00 : 91.00	69.00 : 185.00	43.00 : 185.00
Day-28 - Changes vs Day-0			
no. pts.	5	6	11
Mean	-4.20	12.83	5.09
SD	4.76	14.36	13.83
Median	-3.00	14.00	2.00
Min : Max	-11.00 : 2.00	-9.00 : 33.00	-11.00 : 33.00

Table 30.14: Biochemistry - GGT (U/L) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	23.50	24.83	24.17
SD	13.55	24.17	18.69
Median	21.50	15.50	16.00
Min : Max	10.00 : 44.00	12.00 : 74.00	10.00 : 74.00
Day-14 visit			
no. pts.	6	6	12
Mean	26.50	25.33	25.92
SD	17.49	15.24	15.65
Median	22.50	21.00	21.00
Min : Max	10.00 : 55.00	14.00 : 55.00	10.00 : 55.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	3.00	0.50	1.75
SD	4.43	10.21	7.62
Median	1.50	3.50	1.50
Min : Max	-1.00 : 11.00	-19.00 : 8.00	-19.00 : 11.00
Day-28 visit			
no. pts.	6	6	12
Mean	27.33	55.00	41.17
SD	18.85	66.46	48.76
Median	19.00	23.00	19.50
Min : Max	11.00 : 58.00	16.00 : 185.00	11.00 : 185.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	3.83	30.17	17.00
SD	7.22	69.25	48.91
Median	2.50	3.50	3.00
Min : Max	-6.00 : 14.00	-8.00 : 171.00	-8.00 : 171.00

Table 30.15: Biochemistry - Serum Sodium (mmol/L) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	137.67	137.17	137.42
SD	2.07	5.42	3.92
Median	138.00	139.00	138.00
Min : Max	135.00 : 141.00	130.00 : 143.00	130.00 : 143.00
Day-14 visit			
no. pts.	6	6	12
Mean	139.33	137.00	138.17
SD	3.08	3.03	3.16
Median	138.50	136.50	138.00
Min : Max	136.00 : 145.00	133.00 : 141.00	133.00 : 145.00
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	1.67	-0.17	0.75
SD	2.25	3.19	2.80
Median	2.50	-1.00	1.00
Min : Max	-2.00 : 4.00	-3.00 : 5.00	-3.00 : 5.00
Day-28 visit			
no. pts.	6	6	12
Mean	138.00	137.83	137.92
SD	3.22	3.19	3.06
Median	137.50	138.00	138.00
Min : Max	135.00 : 143.00	133.00 : 142.00	133.00 : 143.00
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.33	0.67	0.50
SD	1.86	4.59	3.34
Median	0.50	-0.50	0.50
Min : Max	-3.00 : 2.00	-3.00 : 9.00	-3.00 : 9.00

Table 30.16: Biochemistry - Potassium (mmol/L) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	4.58	4.56	4.57
SD	0.63	0.67	0.62
Median	4.75	4.65	4.75
Min : Max	3.40 : 5.20	3.50 : 5.37	3.40 : 5.37
Day-14 visit			
no. pts.	6	6	12
Mean	4.65	4.71	4.68
SD	0.77	0.75	0.73
Median	4.85	4.65	4.65
Min : Max	3.30 : 5.30	3.90 : 5.60	3.30 : 5.60
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.07	0.15	0.11
SD	0.36	1.06	0.76
Median	-0.00	-0.06	-0.00
Min : Max	-0.30 : 0.70	-1.00 : 2.10	-1.00 : 2.10
Day-28 visit			
no. pts.	6	6	12
Mean	4.37	4.50	4.43
SD	0.59	0.62	0.58
Median	4.45	4.50	4.50
Min : Max	3.30 : 5.00	3.80 : 5.50	3.30 : 5.50
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.22	-0.06	-0.14
SD	0.28	0.66	0.49
Median	-0.15	-0.05	-0.15
Min : Max	-0.60 : 0.10	-1.00 : 1.00	-1.00 : 1.00

Table 30.17: Biochemistry - Calcium (mmol/L) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	2.36	2.20	2.28
SD	0.32	0.24	0.29
Median	2.25	2.21	2.22
Min : Max	2.10 : 2.97	1.82 : 2.50	1.82 : 2.97
Day-14 visit			
no. pts.	6	6	12
Mean	2.27	2.18	2.22
SD	0.10	0.15	0.13
Median	2.27	2.08	2.21
Min : Max	2.15 : 2.37	2.07 : 2.40	2.07 : 2.40
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.09	-0.02	-0.06
SD	0.35	0.15	0.26
Median	0.04	-0.06	0.01
Min : Max	-0.80 : 0.15	-0.15 : 0.25	-0.80 : 0.25
Day-28 visit			
no. pts.	6	6	12
Mean	2.22	2.23	2.22
SD	0.18	0.23	0.19
Median	2.20	2.18	2.18
Min : Max	2.00 : 2.42	1.95 : 2.62	1.95 : 2.62
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.14	0.03	-0.05
SD	0.41	0.13	0.31
Median	-0.01	0.10	0.04
Min : Max	-0.97 : 0.12	-0.18 : 0.12	-0.97 : 0.12

Table 30.18: Biochemistry - Phosphorus (mmol/L) - Changes vs Day-0 visit - Patients with a complete treatment

	Group A	Group B	All
Day-0 visit			
no. pts.	6	6	12
Mean	1.73	1.69	1.71
SD	0.28	0.29	0.27
Median	1.76	1.59	1.69
Min : Max	1.32 : 2.03	1.42 : 2.13	1.32 : 2.13
Day-14 visit			
no. pts.	6	6	12
Mean	1.81	1.64	1.72
SD	0.37	0.42	0.39
Median	1.65	1.77	1.73
Min : Max	1.45 : 2.29	1.03 : 2.16	1.03 : 2.29
Day-14 - Changes vs Day-0			
no. pts.	6	6	12
Mean	0.08	-0.05	0.01
SD	0.26	0.28	0.27
Median	0.11	-0.06	0.06
Min : Max	-0.29 : 0.45	-0.45 : 0.36	-0.45 : 0.45
Day-28 visit			
no. pts.	6	6	12
Mean	1.68	1.74	1.71
SD	0.41	0.36	0.37
Median	1.61	1.81	1.70
Min : Max	1.10 : 2.36	1.19 : 2.13	1.10 : 2.36
Day-28 - Changes vs Day-0			
no. pts.	6	6	12
Mean	-0.04	0.04	0.00
SD	0.24	0.17	0.20
Median	-0.05	0.05	0.00
Min : Max	-0.36 : 0.32	-0.23 : 0.26	-0.36 : 0.32

Table 31: Clinical parameters - All visits - Weight (kg) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	76.50	81.15	78.83
SD	17.25	13.14	14.82
Median	74.50	85.00	81.25
Min : Max	53.00 : 97.00	63.40 : 98.00	53.00 : 98.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	76.75	81.12	78.93
SD	17.70	13.98	15.38
Median	77.00	84.50	81.50
Min : Max	50.50 : 97.00	62.70 : 100.00	50.50 : 100.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	75.17	80.87	78.02
SD	17.44	12.87	14.91
Median	75.75	84.00	82.00
Min : Max	49.00 : 96.50	62.70 : 98.00	49.00 : 98.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	75.50	81.83	78.67
SD	16.92	12.93	14.73
Median	76.00	86.25	82.75
Min : Max	50.00 : 95.00	64.50 : 98.00	50.00 : 98.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	75.50	82.32	78.91
SD	16.95	11.98	14.44
Median	75.25	85.00	81.25
Min : Max	51.00 : 94.50	68.40 : 99.00	51.00 : 99.00

Table 32: Clinical parameters - All visits - Systolic Blood Pressure (mmHg) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	134.17	131.67	132.92
SD	22.23	14.72	18.02
Median	132.50	135.00	135.00
Min : Max	110.00 : 165.00	110.00 : 150.00	110.00 : 165.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	145.00	138.17	141.58
SD	17.61	9.85	14.06
Median	150.00	137.50	145.50
Min : Max	120.00 : 170.00	128.00 : 150.00	120.00 : 170.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	135.00	132.50	133.75
SD	16.73	15.08	15.24
Median	137.50	135.00	135.00
Min : Max	105.00 : 150.00	105.00 : 150.00	105.00 : 150.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	139.17	139.17	139.17
SD	16.86	12.81	14.28
Median	140.00	140.00	140.00
Min : Max	115.00 : 160.00	120.00 : 155.00	115.00 : 160.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	132.50	141.67	137.08
SD	14.05	18.07	16.16
Median	140.00	145.00	140.00
Min : Max	110.00 : 145.00	110.00 : 160.00	110.00 : 160.00

Table 33: Clinical parameters - All visits - Diastolic Blood Pressure (mmHg) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	81.67	78.33	80.00
SD	8.16	10.33	9.05
Median	80.00	80.00	80.00
Min : Max	70.00 : 95.00	65.00 : 95.00	65.00 : 95.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	75.83	77.50	76.67
SD	12.01	9.87	10.52
Median	80.00	75.00	80.00
Min : Max	55.00 : 90.00	70.00 : 95.00	55.00 : 95.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	80.00	80.83	80.42
SD	8.37	12.01	9.88
Median	77.50	80.00	80.00
Min : Max	70.00 : 90.00	60.00 : 95.00	60.00 : 95.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	70.00	80.83	75.42
SD	11.40	12.01	12.52
Median	67.50	77.50	72.50
Min : Max	60.00 : 90.00	70.00 : 100.00	60.00 : 100.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	75.83	81.67	78.75
SD	7.36	11.69	9.80
Median	72.50	80.00	77.50
Min : Max	70.00 : 85.00	70.00 : 100.00	70.00 : 100.00

Table 34: Clinical parameters - All visits - Heart Rate (bpm) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	64.50	76.50	70.50
SD	9.95	11.81	12.15
Median	67.00	76.00	74.00
Min : Max	50.00 : 75.00	56.00 : 90.00	50.00 : 90.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	63.33	77.17	70.25
SD	9.14	17.36	15.07
Median	62.50	77.50	64.50
Min : Max	51.00 : 79.00	53.00 : 96.00	51.00 : 96.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	66.50	71.67	69.08
SD	11.84	15.24	13.29
Median	68.50	76.00	69.50
Min : Max	53.00 : 85.00	48.00 : 85.00	48.00 : 85.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	67.00	76.17	71.58
SD	11.88	15.79	14.16
Median	64.50	79.00	65.00
Min : Max	55.00 : 90.00	56.00 : 98.00	55.00 : 98.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	67.67	70.83	69.25
SD	16.26	12.50	13.92
Median	66.50	69.00	69.00
Min : Max	50.00 : 96.00	56.00 : 87.00	50.00 : 96.00

Table 35: Clinical parameters - All visits - Diuresis (L/day) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	1.63	1.62	1.62
SD	0.63	0.68	0.63
Median	1.43	1.93	1.68
Min : Max	1.10 : 2.70	0.55 : 2.20	0.55 : 2.70
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	1.78	1.78	1.78
SD	0.47	0.68	0.56
Median	1.75	1.90	1.90
Min : Max	1.20 : 2.50	0.60 : 2.50	0.60 : 2.50
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	1.58	1.70	1.64
SD	0.48	0.66	0.56
Median	1.50	1.80	1.70
Min : Max	1.10 : 2.30	0.50 : 2.50	0.50 : 2.50
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	1.59	1.66	1.63
SD	0.54	0.74	0.62
Median	1.48	1.90	1.78
Min : Max	1.10 : 2.50	0.40 : 2.50	0.40 : 2.50
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	1.66	1.56	1.61
SD	0.51	0.59	0.53
Median	1.55	1.73	1.63
Min : Max	1.10 : 2.60	0.50 : 2.10	0.50 : 2.60

Table 36: Clinical parameters - All visits - Signs of hyperhydratation - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
No	6(100.0%)	6(100.0%)	12(100.0%)
INTERVENTION period			
Visit 2 (day 14)			
No	6(100.0%)	6(100.0%)	12(100.0%)
Visit 3 (day 28)			
Yes		1 (16.7%)	1 (8.3%)
No	6(100.0%)	5 (83.3%)	11 (91.7%)
FOLLOW UP period			
Visit 4 (day 42)			
No	6(100.0%)	6(100.0%)	12(100.0%)
Visit 5 (day 56)			
No	6(100.0%)	6(100.0%)	12(100.0%)

Table 37: Functional parameters - All visits - Weekly Total Urea Kt/V - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	1.35	1.27	1.31
SD	0.23	0.29	0.25
Median	1.34	1.30	1.30
Min : Max	1.10 : 1.68	0.76 : 1.59	0.76 : 1.68
INTERVENTION period			
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	1.38	1.45	1.41
SD	0.26	0.22	0.23
Median	1.42	1.50	1.44
Min : Max	1.07 : 1.70	1.12 : 1.75	1.07 : 1.75
FOLLOW UP period			
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	1.36	1.16	1.26
SD	0.30	0.59	0.46
Median	1.32	1.35	1.35
Min : Max	1.06 : 1.84	0.00 : 1.58	0.00 : 1.84

Table 38: Functional parameters - All visits - Peritoneal equilibration test (PET) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	0.51	0.64	0.57
SD	0.15	0.07	0.13
Median	0.57	0.64	0.60
Min : Max	0.22 : 0.62	0.53 : 0.71	0.22 : 0.71
INTERVENTION period			
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	0.64	0.65	0.64
SD	0.05	0.07	0.06
Median	0.62	0.66	0.64
Min : Max	0.59 : 0.72	0.56 : 0.74	0.56 : 0.74
FOLLOW UP period			
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	0.58	0.54	0.56
SD	0.07	0.27	0.19
Median	0.57	0.65	0.60
Min : Max	0.51 : 0.70	0.00 : 0.70	0.00 : 0.70

Table 39: Functional parameters - All visits - Weekly total creatinine clearance - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	73.37	63.40	68.38
SD	17.06	15.05	16.20
Median	77.90	62.04	67.42
Min : Max	50.03 : 93.39	43.28 : 86.94	43.28 : 93.39
INTERVENTION period			
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	76.53	65.66	71.09
SD	23.91	18.93	21.33
Median	79.90	65.70	67.85
Min : Max	42.38 : 105.74	42.69 : 98.15	42.38 : 105.74
FOLLOW UP period			
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	71.58	54.17	62.88
SD	25.56	29.37	27.78
Median	62.46	65.27	63.79
Min : Max	42.60 : 112.38	0.00 : 80.70	0.00 : 112.38

Table 40: Ultrafiltration - All visits - 1st Daily Bag (mL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	158.33	425.00	291.67
SD	142.89	571.62	420.95
Median	175.00	125.00	125.00
Min : Max	0.00 : 300.00	50.00 : 1500.0	0.00 : 1500.0
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	208.33	266.67	237.50
SD	91.74	254.30	184.79
Median	225.00	150.00	175.00
Min : Max	100.00 : 300.00	50.00 : 700.00	50.00 : 700.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	200.00	350.00	275.00
SD	89.44	415.93	297.34
Median	200.00	125.00	175.00
Min : Max	100.00 : 300.00	50.00 : 1000.0	50.00 : 1000.0
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	341.67	216.67	279.17
SD	304.00	242.21	270.07
Median	275.00	125.00	200.00
Min : Max	0.00 : 900.00	50.00 : 700.00	0.00 : 900.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	350.00	350.00	350.00
SD	207.36	349.28	273.86
Median	350.00	175.00	300.00
Min : Max	0.00 : 600.00	100.00 : 1000.0	0.00 : 1000.0

Table 41: Ultrafiltration - All visits - 2nd Daily Bag (mL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	0.00	16.67	8.33
SD	0.00	112.55	76.38
Median	0.00	50.00	0.00
Min : Max	0.00 : 0.00	-200.0 : 100.00	-200.0 : 100.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	0.00	150.00	75.00
SD	0.00	200.00	155.94
Median	0.00	100.00	0.00
Min : Max	0.00 : 0.00	0.00 : 550.00	0.00 : 550.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	0.00	233.33	116.67
SD	0.00	402.08	297.21
Median	0.00	100.00	0.00
Min : Max	0.00 : 0.00	0.00 : 1050.0	0.00 : 1050.0
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	0.00	241.67	120.83
SD	0.00	423.58	312.22
Median	0.00	75.00	0.00
Min : Max	0.00 : 0.00	0.00 : 1100.0	0.00 : 1100.0
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	0.00	116.67	58.33
SD	0.00	75.28	79.30
Median	0.00	100.00	0.00
Min : Max	0.00 : 0.00	0.00 : 200.00	0.00 : 200.00

Table 42: Ultrafiltration - All visits - 3rd Daily Bag (mL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	0.00	0.00	0.00
SD	0.00	0.00	0.00
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	0.00	0.00	0.00
SD	0.00	0.00	0.00
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	0.00	0.00	0.00
SD	0.00	0.00	0.00
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	0.00	83.33	41.67
SD	0.00	132.92	99.62
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	0.00 : 300.00	0.00 : 300.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	0.00	8.33	4.17
SD	0.00	20.41	14.43
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	0.00 : 50.00	0.00 : 50.00

Table 43: Ultrafiltration - All visits - Nocturnal Bag (mL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	0.00	108.33	54.17
SD	0.00	146.34	113.73
Median	0.00	175.00	0.00
Min : Max	0.00 : 0.00	-100.0 : 250.00	-100.0 : 250.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	0.00	91.67	45.83
SD	0.00	115.83	91.60
Median	0.00	100.00	0.00
Min : Max	0.00 : 0.00	-100.0 : 250.00	-100.0 : 250.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	0.00	-75.00	-37.50
SD	0.00	492.70	334.48
Median	0.00	125.00	0.00
Min : Max	0.00 : 0.00	-1050 : 250.00	-1050 : 250.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	0.00	166.67	83.33
SD	0.00	125.17	121.23
Median	0.00	150.00	0.00
Min : Max	0.00 : 0.00	0.00 : 350.00	0.00 : 350.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	0.00	141.67	70.83
SD	0.00	106.85	103.26
Median	0.00	175.00	0.00
Min : Max	0.00 : 0.00	-50.00 : 250.00	-50.00 : 250.00

Table 44: Ultrafiltration - All visits - Total ultrafiltration (mL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	158.33	550.00	354.17
SD	142.89	467.97	388.15
Median	175.00	400.00	300.00
Min : Max	0.00 : 300.00	300.00 : 1500.0	0.00 : 1500.0
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	208.33	508.33	358.33
SD	91.74	307.27	267.00
Median	225.00	350.00	300.00
Min : Max	100.00 : 300.00	300.00 : 1050.0	100.00 : 1050.0
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	200.00	508.33	354.17
SD	89.44	297.35	264.11
Median	200.00	350.00	300.00
Min : Max	100.00 : 300.00	300.00 : 1000.0	100.00 : 1000.0
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	341.67	708.33	525.00
SD	304.00	475.83	426.13
Median	275.00	550.00	350.00
Min : Max	0.00 : 900.00	300.00 : 1500.0	0.00 : 1500.0
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	350.00	616.67	483.33
SD	207.36	314.11	289.46
Median	350.00	525.00	425.00
Min : Max	0.00 : 600.00	300.00 : 1150.0	0.00 : 1150.0

Table 45: CA_125 (U.a./mL) - All visits - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	78.02	47.23	62.63
SD	53.68	27.88	43.84
Median	57.00	50.05	53.60
Min : Max	42.90 : 184.00	9.90 : 88.60	9.90 : 184.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	81.40	43.58	62.49
SD	60.15	20.73	47.22
Median	59.85	51.85	54.35
Min : Max	45.30 : 203.10	10.90 : 62.00	10.90 : 203.10
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	95.48	71.58	83.53
SD	56.85	51.01	52.99
Median	71.65	70.20	70.80
Min : Max	60.90 : 209.20	11.90 : 145.90	11.90 : 209.20
FOLLOW UP period			
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	82.13	69.32	75.73
SD	71.09	42.69	56.31
Median	55.30	83.75	67.05
Min : Max	39.50 : 224.70	10.70 : 110.90	10.70 : 224.70

Table 46: Proteins in ultrafiltration (mg/L) - All visits - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	0.80	1.15	0.98
SD	0.00	0.76	0.55
Median	0.80	0.80	0.80
Min : Max	0.80 : 0.80	0.30 : 2.20	0.30 : 2.20
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	5	11
Mean	0.80	0.82	0.81
SD	0.00	0.84	0.53
Median	0.80	0.80	0.80
Min : Max	0.80 : 0.80	0.00 : 2.20	0.00 : 2.20
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	0.80	1.02	0.91
SD	0.00	0.80	0.55
Median	0.80	0.80	0.80
Min : Max	0.80 : 0.80	0.30 : 2.60	0.30 : 2.60
FOLLOW UP period			
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	0.80	0.62	0.71
SD	0.00	0.29	0.22
Median	0.80	0.80	0.80
Min : Max	0.80 : 0.80	0.20 : 0.80	0.20 : 0.80

Table 47: Uric Acid (mg/dL) - All visits - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	5.88	5.15	5.52
SD	2.14	1.95	1.99
Median	5.20	4.65	4.70
Min : Max	4.30 : 9.90	3.30 : 8.90	3.30 : 9.90
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	5.23	5.58	5.41
SD	1.26	2.53	1.91
Median	4.75	5.15	4.75
Min : Max	4.20 : 7.50	2.70 : 9.70	2.70 : 9.70
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	5.42	5.63	5.53
SD	1.24	1.72	1.43
Median	5.25	5.35	5.35
Min : Max	4.10 : 6.90	3.50 : 7.70	3.50 : 7.70
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	5.97	5.35	5.66
SD	1.20	1.06	1.12
Median	5.60	5.05	5.15
Min : Max	4.80 : 7.50	4.40 : 7.20	4.40 : 7.50
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	5.87	5.07	5.47
SD	0.81	1.13	1.02
Median	5.60	4.90	5.30
Min : Max	5.20 : 7.30	3.90 : 6.80	3.90 : 7.30

Table 48: Lactic Acid (mg/dL) - All visits - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	10.87	6.63	8.75
SD	5.20	5.73	5.67
Median	9.50	6.00	8.10
Min : Max	7.00 : 21.00	0.70 : 15.30	0.70 : 21.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	5	6	11
Mean	11.60	7.64	9.44
SD	5.92	6.23	6.14
Median	9.90	7.45	9.90
Min : Max	5.00 : 19.80	0.90 : 14.95	0.90 : 19.80
Visit 3 (day 28)			
no. pts.	6	5	11
Mean	10.22	9.12	9.72
SD	2.70	5.92	4.24
Median	10.50	9.00	10.00
Min : Max	7.00 : 13.50	0.60 : 17.11	0.60 : 17.11
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	5	6	11
Mean	11.54	7.32	9.24
SD	5.97	5.47	5.84
Median	13.00	8.50	9.00
Min : Max	5.40 : 19.80	0.60 : 14.40	0.60 : 19.80
Visit 5 (day 56)			
no. pts.	6	5	11
Mean	11.32	7.39	9.53
SD	5.47	7.10	6.27
Median	8.95	6.00	8.00
Min : Max	6.00 : 20.00	0.80 : 17.74	0.80 : 20.00

Table 49: Functional parameters - Changes vs Day 0/Day 28 - Weekly total urea (Kt/V) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Baseline (Day 0)			
no. pts.	6	6	12
Mean	1.35	1.27	1.31
SD	0.23	0.29	0.25
Median	1.34	1.30	1.30
Min : Max	1.10 : 1.68	0.76 : 1.59	0.76 : 1.68
Day 28 - Changes vs Day 0			
no. pts.	6	6	12
Mean	0.03	0.18	0.11
SD	0.15	0.30	0.24
Median	0.01	0.10	0.07
Min : Max	-0.16 : 0.30	-0.11 : 0.76	-0.16 : 0.76
Day 56 - Changes vs Day 0			
no. pts.	6	6	12
Mean	0.01	-0.10	-0.05
SD	0.32	0.64	0.49
Median	-0.07	-0.06	-0.07
Min : Max	-0.38 : 0.41	-1.20 : 0.82	-1.20 : 0.82
Day 56 - Changes vs Day 28			
no. pts.	6	6	12
Mean	-0.02	-0.29	-0.15
SD	0.29	0.50	0.41
Median	0.02	-0.15	-0.06
Min : Max	-0.43 : 0.42	-1.29 : 0.06	-1.29 : 0.42

Table 50: Functional parameters - Changes vs Day 0/Day 28 - Peritoneal equilibration test (PET) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Baseline (Day 0)			
no. pts.	6	6	12
Mean	0.51	0.64	0.57
SD	0.15	0.07	0.13
Median	0.57	0.64	0.60
Min : Max	0.22 : 0.62	0.53 : 0.71	0.22 : 0.71
Day 28 - Changes vs Day 0			
no. pts.	6	6	12
Mean	0.12	0.02	0.07
SD	0.19	0.07	0.15
Median	0.04	0.04	0.04
Min : Max	0.01 : 0.50	-0.12 : 0.08	-0.12 : 0.50
Day 56 - Changes vs Day 0			
no. pts.	6	6	12
Mean	0.07	-0.10	-0.01
SD	0.21	0.31	0.27
Median	0.03	0.02	0.02
Min : Max	-0.10 : 0.48	-0.71 : 0.09	-0.71 : 0.48
Day 56 - Changes vs Day 28			
no. pts.	6	6	12
Mean	-0.05	-0.11	-0.08
SD	0.06	0.29	0.20
Median	-0.04	-0.00	-0.03
Min : Max	-0.15 : 0.02	-0.71 : 0.04	-0.71 : 0.04

Table 51: Functional parameters - Changes vs Day 0/Day 28 - Weekly total creatinine clearance - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Baseline (Day 0)			
no. pts.	6	6	12
Mean	73.37	63.40	68.38
SD	17.06	15.05	16.20
Median	77.90	62.04	67.42
Min : Max	50.03 : 93.39	43.28 : 86.94	43.28 : 93.39
Day 28 - Changes vs Day 0			
no. pts.	6	6	12
Mean	3.16	2.26	2.71
SD	16.64	6.63	12.09
Median	6.03	1.18	2.36
Min : Max	-22.59 : 24.79	-6.39 : 11.21	-22.59 : 24.79
Day 56 - Changes vs Day 0			
no. pts.	6	6	12
Mean	-1.79	-9.23	-5.50
SD	17.79	22.53	19.74
Median	-4.65	-2.23	-2.93
Min : Max	-19.70 : 26.86	-53.87 : 9.52	-53.87 : 26.86
Day 56 - Changes vs Day 28			
no. pts.	6	6	12
Mean	-4.94	-11.49	-8.22
SD	14.39	21.07	17.54
Median	-6.99	-1.56	-1.56
Min : Max	-21.49 : 16.60	-51.85 : 2.39	-51.85 : 16.60

Table 52: Ultrafiltration - Changes vs Day 0/Day 28 - Total ultrafiltration (mL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Baseline (Day 0)			
no. pts.	6	6	12
Mean	158.33	550.00	354.17
SD	142.89	467.97	388.15
Median	175.00	400.00	300.00
Min : Max	0.00 : 300.00	300.00 : 1500.0	0.00 : 1500.0
Day 28 - Changes vs Day 0			
no. pts.	6	6	12
Mean	41.67	-41.67	0.00
SD	102.06	272.79	201.13
Median	25.00	0.00	0.00
Min : Max	-100.0 : 200.00	-500.0 : 350.00	-500.0 : 350.00
Day 56 - Changes vs Day 0			
no. pts.	6	6	12
Mean	191.67	66.67	129.17
SD	149.72	263.94	214.75
Median	200.00	25.00	125.00
Min : Max	0.00 : 400.00	-350.0 : 400.00	-350.0 : 400.00
Day 56 - Changes vs Day 28			
no. pts.	6	6	12
Mean	150.00	108.33	129.17
SD	176.07	115.83	143.75
Median	200.00	100.00	150.00
Min : Max	-100.0 : 400.00	0.00 : 300.00	-100.0 : 400.00

Table 53: CA_125 (U.a./mL) - Changes vs Day 0/Day 28 - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Baseline (Day 0)			
no. pts.	6	6	12
Mean	78.02	47.23	62.63
SD	53.68	27.88	43.84
Median	57.00	50.05	53.60
Min : Max	42.90 : 184.00	9.90 : 88.60	9.90 : 184.00
Day 28 - Changes vs Day 0			
no. pts.	6	6	12
Mean	17.47	24.35	20.91
SD	17.06	34.16	25.99
Median	19.95	16.85	17.75
Min : Max	-13.10 : 32.50	-2.10 : 91.30	-13.10 : 91.30
Day 56 - Changes vs Day 0			
no. pts.	6	6	12
Mean	4.12	22.08	13.10
SD	27.10	25.03	26.58
Median	-4.15	16.70	1.45
Min : Max	-28.10 : 40.70	-1.60 : 56.30	-28.10 : 56.30
Day 56 - Changes vs Day 28			
no. pts.	6	6	12
Mean	-13.35	-2.27	-7.81
SD	18.72	22.76	20.69
Median	-17.15	-0.35	-8.10
Min : Max	-35.70 : 15.50	-35.00 : 30.70	-35.70 : 30.70

Table 54: Proteins in ultrafiltration (mg/L) - Changes vs Day 0/Day 28 - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Baseline (Day 0)			
no. pts.	6	6	12
Mean	0.80	1.15	0.98
SD	0.00	0.76	0.55
Median	0.80	0.80	0.80
Min : Max	0.80 : 0.80	0.30 : 2.20	0.30 : 2.20
Day 28 - Changes vs Day 0			
no. pts.	6	6	12
Mean	0.00	-0.13	-0.07
SD	0.00	1.42	0.96
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	-1.70 : 2.30	-1.70 : 2.30
Day 56 - Changes vs Day 0			
no. pts.	6	6	12
Mean	0.00	-0.53	-0.27
SD	0.00	0.84	0.63
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	-1.80 : 0.00	-1.80 : 0.00
Day 56 - Changes vs Day 28			
no. pts.	6	6	12
Mean	0.00	-0.40	-0.20
SD	0.00	0.93	0.66
Median	0.00	0.00	0.00
Min : Max	0.00 : 0.00	-2.30 : 0.00	-2.30 : 0.00

Table 55: Hematology - All visits - RBC count (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	3.77	3.88	3.83
SD	0.53	0.46	0.47
Median	3.71	3.99	3.92
Min : Max	3.07 : 4.48	3.03 : 4.31	3.03 : 4.48
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	3.73	3.92	3.83
SD	0.35	0.52	0.43
Median	3.71	3.98	3.89
Min : Max	3.22 : 4.13	3.03 : 4.64	3.03 : 4.64
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	3.77	3.64	3.71
SD	0.24	0.53	0.40
Median	3.70	3.59	3.70
Min : Max	3.51 : 4.15	2.92 : 4.28	2.92 : 4.28
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	3.74	3.74	3.74
SD	0.33	0.44	0.37
Median	3.77	3.65	3.68
Min : Max	3.35 : 4.22	3.20 : 4.41	3.20 : 4.41
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	3.66	3.76	3.71
SD	0.46	0.32	0.38
Median	3.76	3.71	3.76
Min : Max	2.95 : 4.26	3.44 : 4.17	2.95 : 4.26

Table 56: Hematology - All visits - Hematocrit (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	34.33	35.23	34.78
SD	4.74	4.32	4.35
Median	34.45	35.85	35.60
Min : Max	27.60 : 42.00	26.90 : 39.10	26.90 : 42.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	33.92	35.40	34.66
SD	2.94	4.62	3.77
Median	33.50	36.45	36.20
Min : Max	29.60 : 37.40	26.50 : 40.20	26.50 : 40.20
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	33.97	32.67	33.32
SD	2.04	4.86	3.62
Median	33.65	32.85	33.65
Min : Max	30.80 : 36.90	25.80 : 39.50	25.80 : 39.50
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	29.92	33.65	31.78
SD	9.41	3.27	6.99
Median	32.80	33.85	33.35
Min : Max	11.80 : 38.10	28.70 : 37.90	11.80 : 38.10
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	33.08	33.95	33.52
SD	3.97	2.68	3.26
Median	33.85	33.00	33.35
Min : Max	25.80 : 37.60	31.40 : 38.80	25.80 : 38.80

Table 57: Hematology - All visits - Hemoglobin (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	11.00	11.22	11.11
SD	1.56	1.18	1.32
Median	11.10	11.55	11.55
Min : Max	8.50 : 13.20	8.90 : 12.20	8.50 : 13.20
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	10.95	11.30	11.13
SD	1.21	1.33	1.23
Median	10.90	11.55	11.35
Min : Max	9.00 : 12.20	8.80 : 12.70	8.80 : 12.70
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	11.02	10.60	10.81
SD	0.78	1.45	1.13
Median	10.90	10.70	10.90
Min : Max	10.10 : 12.20	8.60 : 12.30	8.60 : 12.30
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	14.85	10.83	12.84
SD	9.92	0.90	7.04
Median	10.80	10.95	10.95
Min : Max	9.50 : 35.00	9.30 : 11.80	9.30 : 35.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	10.62	10.97	10.79
SD	1.38	0.68	1.05
Median	10.80	10.90	10.80
Min : Max	8.20 : 12.30	10.10 : 11.90	8.20 : 12.30

Table 58: Hematology - All visits - WBC count (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	7.75	11.49	9.62
SD	3.52	9.93	7.37
Median	6.27	8.23	7.34
Min : Max	4.68 : 14.27	4.19 : 31.21	4.19 : 31.21
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	6.89	12.19	9.54
SD	2.21	11.65	8.46
Median	6.77	8.13	7.90
Min : Max	4.58 : 10.12	5.97 : 35.84	4.58 : 35.84
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	7.18	11.92	9.55
SD	2.19	11.76	8.44
Median	7.04	7.28	7.28
Min : Max	4.90 : 10.61	5.27 : 35.75	4.90 : 35.75
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	6.89	11.11	9.00
SD	2.08	11.19	7.98
Median	7.04	6.46	6.46
Min : Max	4.27 : 9.11	4.75 : 33.75	4.27 : 33.75
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	6.70	10.81	8.76
SD	1.04	9.37	6.71
Median	6.73	7.26	7.10
Min : Max	5.18 : 7.99	5.81 : 29.90	5.18 : 29.90

Table 59: Hematology - All visits - Neutrophils (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	5.52	24.51	15.01
SD	3.17	32.09	23.89
Median	4.44	5.47	4.75
Min : Max	2.52 : 11.35	3.57 : 78.50	2.52 : 78.50
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	4.88	25.11	15.00
SD	1.92	32.18	24.16
Median	4.68	4.62	4.62
Min : Max	2.72 : 7.63	4.07 : 70.80	2.72 : 70.80
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	5.11	26.58	15.85
SD	1.97	31.94	24.31
Median	4.90	7.76	6.08
Min : Max	2.93 : 8.11	4.11 : 73.70	2.93 : 73.70
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	4.68	24.40	14.54
SD	1.76	31.88	23.86
Median	5.10	4.76	4.76
Min : Max	2.50 : 6.52	3.47 : 74.40	2.50 : 74.40
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	4.48	25.87	15.18
SD	1.03	33.43	25.16
Median	4.43	4.83	4.73
Min : Max	3.02 : 5.66	3.26 : 70.70	3.02 : 70.70

Table 60: Hematology - All visits - Basophils (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	0.05	0.19	0.12
SD	0.01	0.21	0.16
Median	0.05	0.08	0.06
Min : Max	0.04 : 0.07	0.01 : 0.50	0.01 : 0.50
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	0.05	0.23	0.14
SD	0.02	0.29	0.22
Median	0.06	0.08	0.06
Min : Max	0.03 : 0.07	0.01 : 0.70	0.01 : 0.70
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	0.05	0.24	0.15
SD	0.02	0.34	0.25
Median	0.06	0.10	0.07
Min : Max	0.02 : 0.07	0.02 : 0.90	0.02 : 0.90
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	0.06	0.44	0.25
SD	0.01	0.59	0.44
Median	0.06	0.10	0.07
Min : Max	0.04 : 0.07	0.02 : 1.20	0.02 : 1.20
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	0.05	0.22	0.13
SD	0.01	0.26	0.20
Median	0.05	0.09	0.06
Min : Max	0.03 : 0.07	0.02 : 0.60	0.02 : 0.60

Table 61: Hematology - All visits - Eosinophils (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	0.34	0.60	0.47
SD	0.20	0.68	0.49
Median	0.30	0.25	0.28
Min : Max	0.14 : 0.65	0.00 : 1.60	0.00 : 1.60
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	0.25	0.90	0.57
SD	0.13	1.09	0.82
Median	0.23	0.29	0.25
Min : Max	0.10 : 0.43	0.00 : 2.40	0.00 : 2.40
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	0.25	0.88	0.56
SD	0.13	1.11	0.82
Median	0.25	0.27	0.25
Min : Max	0.09 : 0.48	0.00 : 2.70	0.00 : 2.70
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	0.33	0.85	0.59
SD	0.22	1.24	0.89
Median	0.32	0.25	0.26
Min : Max	0.08 : 0.66	0.00 : 3.20	0.00 : 3.20
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	0.28	0.87	0.57
SD	0.16	1.09	0.80
Median	0.26	0.25	0.26
Min : Max	0.12 : 0.58	0.00 : 2.50	0.00 : 2.50

Table 62: Hematology - All visits - Lymphocytes (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	1.16	12.19	6.67
SD	0.19	12.97	10.47
Median	1.19	6.89	1.34
Min : Max	0.83 : 1.38	1.28 : 29.60	0.83 : 29.60
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	1.12	13.30	7.21
SD	0.26	12.87	10.76
Median	1.15	10.62	1.38
Min : Max	0.68 : 1.40	1.36 : 30.19	0.68 : 30.19
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	1.15	12.28	6.71
SD	0.11	12.64	10.31
Median	1.19	8.51	1.24
Min : Max	0.96 : 1.25	1.15 : 27.30	0.96 : 27.30
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	1.14	12.83	6.98
SD	0.16	13.42	10.91
Median	1.08	7.99	1.41
Min : Max	1.01 : 1.44	1.37 : 30.20	1.01 : 30.20
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	1.22	11.48	6.35
SD	0.14	11.03	9.17
Median	1.17	9.71	1.54
Min : Max	1.07 : 1.44	1.64 : 25.78	1.07 : 25.78

Table 63: Hematology - All visits - Monocytes (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	0.68	4.79	2.73
SD	0.20	7.35	5.40
Median	0.60	0.64	0.60
Min : Max	0.46 : 1.02	0.48 : 18.50	0.46 : 18.50
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	0.59	3.49	2.04
SD	0.16	4.20	3.21
Median	0.58	1.07	0.72
Min : Max	0.43 : 0.86	0.43 : 10.10	0.43 : 10.10
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	0.62	3.27	1.94
SD	0.13	4.02	3.04
Median	0.58	0.83	0.65
Min : Max	0.49 : 0.85	0.51 : 9.30	0.49 : 9.30
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	0.69	3.58	2.14
SD	0.14	4.71	3.52
Median	0.67	0.73	0.70
Min : Max	0.53 : 0.90	0.32 : 10.10	0.32 : 10.10
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	0.68	3.44	2.06
SD	0.12	4.43	3.32
Median	0.65	0.75	0.66
Min : Max	0.56 : 0.90	0.33 : 9.30	0.33 : 9.30

Table 64: Hematology - All visits - Platelets count (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	242.33	225.50	233.92
SD	46.85	77.98	61.96
Median	225.50	225.00	225.50
Min : Max	187.00 : 301.00	132.00 : 349.00	132.00 : 349.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	249.83	238.17	244.00
SD	53.82	97.02	75.05
Median	225.00	242.50	225.00
Min : Max	205.00 : 342.00	122.00 : 333.00	122.00 : 342.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	261.67	229.00	245.33
SD	46.19	65.97	56.91
Median	240.50	232.00	238.50
Min : Max	226.00 : 344.00	134.00 : 305.00	134.00 : 344.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	237.67	237.33	237.50
SD	31.85	55.64	43.23
Median	230.50	245.50	237.00
Min : Max	204.00 : 289.00	172.00 : 301.00	172.00 : 301.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	258.50	253.67	256.08
SD	43.98	109.35	79.50
Median	242.50	254.00	242.50
Min : Max	214.00 : 314.00	133.00 : 399.00	133.00 : 399.00

Table 65: Biochemistry - All visits - BUN (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	149.20	168.45	158.83
SD	46.95	48.12	46.43
Median	163.50	173.00	167.00
Min : Max	74.20 : 202.00	79.70 : 219.00	74.20 : 219.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	174.00	152.45	163.23
SD	43.24	70.99	57.16
Median	180.00	130.50	154.00
Min : Max	119.00 : 225.00	82.10 : 260.00	82.10 : 260.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	152.62	146.28	149.45
SD	59.32	68.13	61.00
Median	140.50	140.47	140.50
Min : Max	87.74 : 245.00	81.20 : 246.00	81.20 : 246.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	151.41	135.99	143.70
SD	49.20	61.16	53.53
Median	151.50	121.90	139.50
Min : Max	98.47 : 209.00	81.20 : 228.00	81.20 : 228.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	149.13	129.38	139.26
SD	41.02	62.90	51.67
Median	150.50	117.60	143.00
Min : Max	86.80 : 192.00	72.80 : 232.00	72.80 : 232.00

Table 66: Biochemistry - All visits - Creatinine (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	7.60	9.04	8.32
SD	1.89	2.19	2.09
Median	7.68	8.12	8.12
Min : Max	5.64 : 9.96	6.97 : 12.83	5.64 : 12.83
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	7.32	9.68	8.50
SD	1.45	2.47	2.29
Median	7.11	8.79	8.14
Min : Max	5.65 : 9.31	7.62 : 14.12	5.65 : 14.12
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	7.46	9.24	8.35
SD	1.76	2.06	2.05
Median	7.17	8.85	8.39
Min : Max	5.42 : 10.00	7.23 : 12.71	5.42 : 12.71
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	7.96	9.06	8.51
SD	1.81	2.07	1.94
Median	7.44	8.49	8.21
Min : Max	6.12 : 10.93	6.96 : 12.07	6.12 : 12.07
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	7.97	9.19	8.58
SD	2.22	1.75	2.01
Median	7.15	8.68	8.22
Min : Max	5.71 : 11.24	7.19 : 11.80	5.71 : 11.80

Table 67: Biochemistry - All visits - Glucose (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	108.17	114.50	111.33
SD	31.48	26.64	28.00
Median	110.50	116.00	111.00
Min : Max	71.00 : 148.00	87.00 : 141.00	71.00 : 148.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	93.33	104.33	98.83
SD	13.38	21.86	18.21
Median	96.50	95.50	96.50
Min : Max	73.00 : 112.00	82.00 : 136.00	73.00 : 136.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	115.33	140.00	127.67
SD	27.35	50.30	40.69
Median	110.50	123.00	114.00
Min : Max	83.00 : 166.00	92.00 : 222.00	83.00 : 222.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	102.67	110.50	106.58
SD	32.87	20.29	26.36
Median	90.50	108.50	102.50
Min : Max	78.00 : 167.00	86.00 : 147.00	78.00 : 167.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	111.50	121.17	116.33
SD	18.96	40.05	30.30
Median	110.50	116.50	110.50
Min : Max	89.00 : 136.00	83.00 : 193.00	83.00 : 193.00

Table 68: Biochemistry - All visits - Total Choleterol (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	171.67	137.83	154.75
SD	18.42	15.01	23.85
Median	173.00	138.00	152.50
Min : Max	143.00 : 196.00	113.00 : 156.00	113.00 : 196.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	181.33	138.00	159.67
SD	29.74	21.32	33.48
Median	188.50	136.00	148.50
Min : Max	145.00 : 220.00	113.00 : 172.00	113.00 : 220.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	176.00	133.83	154.92
SD	40.79	17.55	37.17
Median	170.00	134.00	141.50
Min : Max	136.00 : 245.00	109.00 : 161.00	109.00 : 245.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	189.17	141.67	165.42
SD	47.15	21.54	42.86
Median	179.50	137.00	155.00
Min : Max	144.00 : 277.00	117.00 : 178.00	117.00 : 277.00
Visit 5 (day 56)			
no. pts.	6	5	11
Mean	176.17	140.80	160.09
SD	39.34	33.34	39.49
Median	172.50	125.00	152.00
Min : Max	134.00 : 236.00	110.00 : 191.00	110.00 : 236.00

Table 69: Biochemistry - All visits - HDL Choleterol (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	37.17	47.00	42.08
SD	11.41	17.56	15.02
Median	34.50	45.50	40.50
Min : Max	25.00 : 52.00	25.00 : 78.00	25.00 : 78.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	36.17	42.83	39.50
SD	7.86	10.21	9.36
Median	35.00	42.00	38.00
Min : Max	28.00 : 50.00	29.00 : 54.00	28.00 : 54.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	36.83	43.17	40.00
SD	10.74	6.71	9.16
Median	34.00	46.00	40.50
Min : Max	27.00 : 56.00	31.00 : 49.00	27.00 : 56.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	37.17	44.17	40.67
SD	10.83	12.12	11.55
Median	36.50	43.50	39.00
Min : Max	25.00 : 51.00	30.00 : 57.00	25.00 : 57.00
Visit 5 (day 56)			
no. pts.	6	5	11
Mean	35.17	39.40	37.09
SD	8.93	6.35	7.80
Median	35.00	38.00	38.00
Min : Max	26.00 : 48.00	33.00 : 49.00	26.00 : 49.00

Table 70: Biochemistry - All visits - LDL Choleterol (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	96.83	65.83	81.33
SD	15.28	11.51	20.70
Median	100.50	72.00	74.00
Min : Max	70.00 : 114.00	47.00 : 75.00	47.00 : 114.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	90.83	65.67	78.25
SD	22.99	14.45	22.54
Median	87.00	70.50	72.00
Min : Max	67.00 : 117.00	37.00 : 77.00	37.00 : 117.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	93.67	65.00	79.33
SD	25.13	12.21	24.06
Median	91.00	68.50	72.50
Min : Max	63.00 : 133.00	43.00 : 79.00	43.00 : 133.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	109.50	74.17	91.83
SD	31.14	15.13	29.76
Median	108.50	76.50	85.00
Min : Max	72.00 : 157.00	51.00 : 91.00	51.00 : 157.00
Visit 5 (day 56)			
no. pts.	6	5	11
Mean	100.83	73.60	88.45
SD	29.98	23.33	29.48
Median	96.00	70.00	79.00
Min : Max	67.00 : 141.00	47.00 : 108.00	47.00 : 141.00

Table 71: Biochemistry - All visits - Triglycerides (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	5	6	11
Mean	167.40	128.67	146.27
SD	112.70	48.25	81.57
Median	131.00	122.50	131.00
Min : Max	85.00 : 364.00	77.00 : 189.00	77.00 : 364.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	5	11
Mean	292.33	149.80	227.55
SD	261.60	77.23	205.29
Median	178.00	112.00	169.00
Min : Max	130.00 : 808.00	66.00 : 244.00	66.00 : 808.00
Visit 3 (day 28)			
no. pts.	5	6	11
Mean	198.00	132.00	162.00
SD	99.89	52.55	81.00
Median	154.00	101.00	128.00
Min : Max	107.00 : 344.00	97.00 : 217.00	97.00 : 344.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	197.33	107.67	152.50
SD	99.54	31.47	84.54
Median	168.00	103.00	134.50
Min : Max	80.00 : 336.00	67.00 : 151.00	67.00 : 336.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	170.83	119.67	145.25
SD	43.77	56.86	55.27
Median	164.50	100.50	150.50
Min : Max	122.00 : 250.00	69.00 : 203.00	69.00 : 250.00

Table 72: Biochemistry - All visits - Total proteins (g/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	6.53	6.10	6.32
SD	0.56	0.51	0.56
Median	6.60	6.10	6.40
Min : Max	5.90 : 7.30	5.50 : 6.70	5.50 : 7.30
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	6.60	6.20	6.40
SD	0.42	0.53	0.50
Median	6.55	6.15	6.50
Min : Max	6.10 : 7.30	5.60 : 6.90	5.60 : 7.30
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	6.55	6.02	6.28
SD	0.34	0.48	0.49
Median	6.65	6.00	6.50
Min : Max	5.90 : 6.90	5.40 : 6.60	5.40 : 6.90
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	6.52	6.13	6.33
SD	0.44	0.67	0.58
Median	6.65	6.10	6.50
Min : Max	5.90 : 7.10	5.40 : 7.10	5.40 : 7.10
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	6.60	5.95	6.28
SD	0.18	0.58	0.53
Median	6.65	5.95	6.40
Min : Max	6.30 : 6.80	5.20 : 6.80	5.20 : 6.80

Table 73: Biochemistry - All visits - Albumin (g/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	3.73	3.36	3.55
SD	0.18	0.73	0.54
Median	3.65	3.55	3.60
Min : Max	3.60 : 4.00	2.00 : 4.10	2.00 : 4.10
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	3.80	3.57	3.68
SD	0.11	0.60	0.43
Median	3.80	3.75	3.80
Min : Max	3.70 : 4.00	2.40 : 4.10	2.40 : 4.10
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	3.24	3.48	3.36
SD	1.47	0.68	1.10
Median	3.75	3.60	3.70
Min : Max	0.25 : 4.00	2.20 : 4.10	0.25 : 4.10
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	3.83	3.63	3.73
SD	0.10	0.60	0.42
Median	3.80	3.75	3.80
Min : Max	3.70 : 4.00	2.50 : 4.20	2.50 : 4.20
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	3.83	3.43	3.63
SD	0.14	0.58	0.45
Median	3.85	3.60	3.80
Min : Max	3.60 : 4.00	2.50 : 4.00	2.50 : 4.00

Table 74: Biochemistry - All visits - Total bilirubin (mg/dL) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	4	10
Mean	0.46	0.61	0.52
SD	0.11	0.26	0.19
Median	0.44	0.64	0.50
Min : Max	0.35 : 0.61	0.30 : 0.86	0.30 : 0.86
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	0.53	0.54	0.54
SD	0.13	0.21	0.17
Median	0.51	0.56	0.51
Min : Max	0.37 : 0.71	0.30 : 0.77	0.30 : 0.77
Visit 3 (day 28)			
no. pts.	6	5	11
Mean	0.39	0.50	0.44
SD	0.13	0.26	0.20
Median	0.34	0.49	0.35
Min : Max	0.25 : 0.57	0.20 : 0.82	0.20 : 0.82
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	0.45	0.52	0.48
SD	0.12	0.21	0.17
Median	0.47	0.51	0.50
Min : Max	0.27 : 0.57	0.25 : 0.83	0.25 : 0.83
Visit 5 (day 56)			
no. pts.	6	5	11
Mean	0.40	0.51	0.45
SD	0.10	0.18	0.14
Median	0.41	0.44	0.44
Min : Max	0.24 : 0.50	0.30 : 0.74	0.24 : 0.74

Table 75: Biochemistry - All visits - SGOT (AST) (U/L) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	5	11
Mean	11.83	14.60	13.09
SD	3.31	4.77	4.09
Median	12.00	15.00	14.00
Min : Max	7.00 : 15.00	8.00 : 20.00	7.00 : 20.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	13.50	15.67	14.58
SD	2.95	3.78	3.42
Median	13.00	16.00	14.50
Min : Max	11.00 : 19.00	9.00 : 20.00	9.00 : 20.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	13.33	14.50	13.92
SD	5.13	4.76	4.76
Median	12.50	15.00	14.50
Min : Max	8.00 : 22.00	7.00 : 21.00	7.00 : 22.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	13.17	15.00	14.08
SD	3.92	4.43	4.10
Median	13.00	15.00	14.50
Min : Max	9.00 : 18.00	9.00 : 21.00	9.00 : 21.00
Visit 5 (day 56)			
no. pts.	6	5	11
Mean	12.00	13.20	12.55
SD	3.69	4.60	3.96
Median	13.00	12.00	13.00
Min : Max	7.00 : 16.00	9.00 : 21.00	7.00 : 21.00

Table 76: Biochemistry - All visits - SGPT (ALT) (U/L) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	5	11
Mean	12.67	15.80	14.09
SD	2.73	6.98	5.09
Median	12.50	16.00	13.00
Min : Max	9.00 : 17.00	9.00 : 27.00	9.00 : 27.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	15.67	25.50	20.58
SD	7.17	16.55	13.20
Median	15.00	20.50	17.50
Min : Max	8.00 : 28.00	9.00 : 54.00	8.00 : 54.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	16.50	19.67	18.08
SD	12.05	10.61	10.95
Median	11.50	16.50	14.00
Min : Max	7.00 : 40.00	7.00 : 34.00	7.00 : 40.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	15.33	20.00	17.67
SD	6.38	8.74	7.69
Median	13.50	17.00	15.00
Min : Max	10.00 : 28.00	9.00 : 32.00	9.00 : 32.00
Visit 5 (day 56)			
no. pts.	6	5	11
Mean	14.00	20.40	16.91
SD	3.46	13.05	9.24
Median	14.00	16.00	15.00
Min : Max	9.00 : 19.00	10.00 : 43.00	9.00 : 43.00

Table 77: Biochemistry - All visits - Alkaline Phosphatase (U/L) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	5	11
Mean	66.17	100.60	81.82
SD	15.79	41.47	33.70
Median	61.50	82.00	73.00
Min : Max	53.00 : 94.00	64.00 : 167.00	53.00 : 167.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	5	5	10
Mean	60.80	110.40	85.60
SD	17.08	32.86	35.96
Median	63.00	111.00	79.00
Min : Max	38.00 : 85.00	73.00 : 161.00	38.00 : 161.00
Visit 3 (day 28)			
no. pts.	5	6	11
Mean	64.60	120.17	94.91
SD	17.42	42.85	43.37
Median	64.00	117.00	86.00
Min : Max	43.00 : 91.00	69.00 : 185.00	43.00 : 185.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	62.83	127.17	95.00
SD	18.06	42.41	45.77
Median	61.50	134.00	80.50
Min : Max	38.00 : 93.00	65.00 : 171.00	38.00 : 171.00
Visit 5 (day 56)			
no. pts.	6	5	11
Mean	66.50	123.80	92.55
SD	20.27	53.56	47.41
Median	62.50	114.00	75.00
Min : Max	44.00 : 102.00	66.00 : 196.00	44.00 : 196.00

Table 78: Biochemistry - All visits - GGT (U/L) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	5	11
Mean	23.50	15.00	19.64
SD	13.55	2.24	10.65
Median	21.50	15.00	16.00
Min : Max	10.00 : 44.00	12.00 : 18.00	10.00 : 44.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	26.50	25.33	25.92
SD	17.49	15.24	15.65
Median	22.50	21.00	21.00
Min : Max	10.00 : 55.00	14.00 : 55.00	10.00 : 55.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	27.33	55.00	41.17
SD	18.85	66.46	48.76
Median	19.00	23.00	19.50
Min : Max	11.00 : 58.00	16.00 : 185.00	11.00 : 185.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	36.00	29.67	32.83
SD	23.04	32.77	27.21
Median	30.00	16.50	19.00
Min : Max	13.00 : 69.00	12.00 : 96.00	12.00 : 96.00
Visit 5 (day 56)			
no. pts.	6	5	11
Mean	26.50	28.40	27.36
SD	16.33	29.18	21.79
Median	22.50	14.00	18.00
Min : Max	12.00 : 55.00	12.00 : 80.00	12.00 : 80.00

Table 79: Biochemistry - All visits - Serum Sodium (mmol/L) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	137.67	137.17	137.42
SD	2.07	5.42	3.92
Median	138.00	139.00	138.00
Min : Max	135.00 : 141.00	130.00 : 143.00	130.00 : 143.00
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	139.33	137.00	138.17
SD	3.08	3.03	3.16
Median	138.50	136.50	138.00
Min : Max	136.00 : 145.00	133.00 : 141.00	133.00 : 145.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	138.00	137.83	137.92
SD	3.22	3.19	3.06
Median	137.50	138.00	138.00
Min : Max	135.00 : 143.00	133.00 : 142.00	133.00 : 143.00
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	138.67	136.33	137.50
SD	4.68	3.20	4.01
Median	137.00	137.00	137.00
Min : Max	134.00 : 145.00	132.00 : 140.00	132.00 : 145.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	114.97	136.33	125.65
SD	54.49	3.98	38.49
Median	136.00	136.50	136.00
Min : Max	3.80 : 141.00	131.00 : 141.00	3.80 : 141.00

Table 80: Biochemistry - All visits - Potassium (mmol/L) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	4.58	4.56	4.57
SD	0.63	0.67	0.62
Median	4.75	4.65	4.75
Min : Max	3.40 : 5.20	3.50 : 5.37	3.40 : 5.37
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	4.65	4.71	4.68
SD	0.77	0.75	0.73
Median	4.85	4.65	4.65
Min : Max	3.30 : 5.30	3.90 : 5.60	3.30 : 5.60
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	4.37	4.50	4.43
SD	0.59	0.62	0.58
Median	4.45	4.50	4.50
Min : Max	3.30 : 5.00	3.80 : 5.50	3.30 : 5.50
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	4.65	4.68	4.67
SD	0.66	0.62	0.61
Median	4.70	4.65	4.65
Min : Max	3.50 : 5.30	3.80 : 5.50	3.50 : 5.50
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	4.43	4.45	4.44
SD	0.69	0.52	0.58
Median	4.60	4.45	4.60
Min : Max	3.50 : 5.20	3.80 : 5.30	3.50 : 5.30

Table 81: Biochemistry - All visits - Calcium (mmol/L) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	2.36	2.20	2.28
SD	0.32	0.24	0.29
Median	2.25	2.21	2.22
Min : Max	2.10 : 2.97	1.82 : 2.50	1.82 : 2.97
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	2.27	2.18	2.22
SD	0.10	0.15	0.13
Median	2.27	2.08	2.21
Min : Max	2.15 : 2.37	2.07 : 2.40	2.07 : 2.40
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	2.22	2.23	2.22
SD	0.18	0.23	0.19
Median	2.20	2.18	2.18
Min : Max	2.00 : 2.42	1.95 : 2.62	1.95 : 2.62
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	2.27	2.23	2.25
SD	0.16	0.22	0.18
Median	2.21	2.16	2.17
Min : Max	2.12 : 2.52	2.00 : 2.62	2.00 : 2.62
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	2.17	2.17	2.17
SD	0.06	0.08	0.07
Median	2.17	2.16	2.16
Min : Max	2.10 : 2.25	2.07 : 2.30	2.07 : 2.30

Table 82: Biochemistry - All visits - Phosphorus (mmol/L) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	1.73	1.69	1.71
SD	0.28	0.29	0.27
Median	1.76	1.59	1.69
Min : Max	1.32 : 2.03	1.42 : 2.13	1.32 : 2.13
INTERVENTION period			
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	1.81	1.64	1.72
SD	0.37	0.42	0.39
Median	1.65	1.77	1.73
Min : Max	1.45 : 2.29	1.03 : 2.16	1.03 : 2.29
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	1.68	1.74	1.71
SD	0.41	0.36	0.37
Median	1.61	1.81	1.70
Min : Max	1.10 : 2.36	1.19 : 2.13	1.10 : 2.36
FOLLOW UP period			
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	1.79	1.73	1.76
SD	0.32	0.30	0.30
Median	1.91	1.76	1.79
Min : Max	1.29 : 2.07	1.23 : 2.07	1.23 : 2.07
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	1.74	1.85	1.79
SD	0.29	0.22	0.25
Median	1.70	1.86	1.79
Min : Max	1.45 : 2.10	1.49 : 2.10	1.45 : 2.10

Table 83: All visits - Subjective questionnaire (Total score) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	18.83	17.50	18.17
SD	4.07	2.51	3.30
Median	18.00	17.00	17.00
Min : Max	14.00 : 25.00	15.00 : 21.00	14.00 : 25.00
INTERVENTION period			
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	18.33	19.50	18.92
SD	1.51	5.01	3.58
Median	18.00	18.00	18.00
Min : Max	17.00 : 21.00	15.00 : 26.00	15.00 : 26.00
FOLLOW UP period			
Visit 5 (day 56)			
no. pts.	6	5	11
Mean	16.50	18.40	17.36
SD	1.64	4.67	3.32
Median	16.00	15.00	16.00
Min : Max	15.00 : 19.00	15.00 : 24.00	15.00 : 24.00

Table 84: Changes vs Day 0/Day 28 - Subjective questionnaire (Total score) - Mean values - Patients with a complete treatment

	Group A No. pts (%)	Group B No. pts (%)	All No. pts (%)
Baseline (Day 0)			
no. pts.	6	6	12
Mean	18.83	17.50	18.17
SD	4.07	2.51	3.30
Median	18.00	17.00	17.00
Min : Max	14.00 : 25.00	15.00 : 21.00	14.00 : 25.00
Day 28 - Changes vs Day 0			
no. pts.	6	6	12
Mean	-0.50	2.00	0.75
SD	4.68	2.76	3.89
Median	-0.50	1.50	0.50
Min : Max	-7.00 : 5.00	-1.00 : 6.00	-7.00 : 6.00
Day 56 - Changes vs Day 0			
no. pts.	6	5	11
Mean	-2.33	1.40	-0.64
SD	4.08	3.13	4.01
Median	-2.00	0.00	0.00
Min : Max	-7.00 : 2.00	-2.00 : 6.00	-7.00 : 6.00
Day 56 - Changes vs Day 28			
no. pts.	6	5	11
Mean	-1.83	0.20	-0.91
SD	1.17	1.64	1.70
Median	-2.00	0.00	-1.00
Min : Max	-3.00 : 0.00	-1.00 : 3.00	-3.00 : 3.00

Table 85 : Serum - L-carnitine [µmol/l] - Patients with a complete treatment

	Group A	Group B	All
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	59.00	43.17	51.08
SD	31.10	13.66	24.35
Median	50.50	44.50	46.50
Min : Max	36.00 : 119.00	20.00 : 62.00	20.00 : 119.00
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	173.83	212.33	193.08
SD	37.66	54.47	48.96
Median	186.00	233.50	196.50
Min : Max	114.00 : 211.00	137.00 : 262.00	114.00 : 262.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	128.00	170.83	149.42
SD	30.67	39.66	40.53
Median	129.00	187.50	147.00
Min : Max	77.00 : 161.00	107.00 : 206.00	77.00 : 206.00
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	66.50	66.50	66.50
SD	10.93	15.83	12.97
Median	70.50	66.00	69.00
Min : Max	48.00 : 76.00	47.00 : 88.00	47.00 : 88.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	64.33	53.67	59.00
SD	11.91	8.98	11.50
Median	59.50	51.50	57.00
Min : Max	55.00 : 86.00	45.00 : 66.00	45.00 : 86.00

Table 86 : Serum - Acetyl-L-carnitine [µmol/l] - Patients with a complete treatment

	Group A	Group B	All
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	10.17	9.00	9.58
SD	4.58	4.56	4.40
Median	8.50	8.00	8.00
Min : Max	7.00 : 19.00	5.00 : 18.00	5.00 : 19.00
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	28.67	41.67	35.17
SD	9.85	24.77	19.21
Median	29.00	36.50	31.50
Min : Max	14.00 : 41.00	17.00 : 79.00	14.00 : 79.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	24.33	45.00	34.67
SD	10.23	19.16	18.19
Median	24.50	38.50	31.50
Min : Max	12.00 : 39.00	24.00 : 71.00	12.00 : 71.00
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	11.33	12.67	12.00
SD	4.84	4.89	4.69
Median	10.00	12.00	11.00
Min : Max	5.00 : 18.00	6.00 : 20.00	5.00 : 20.00
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	9.33	11.00	10.17
SD	2.07	4.15	3.24
Median	9.00	10.00	9.50
Min : Max	7.00 : 13.00	7.00 : 19.00	7.00 : 19.00

Table 87 : Urine - L-carnitine [µmol] - Patients with a complete treatment

	Group A	Group B	All
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	127.73	50.66	89.19
SD	134.56	50.03	104.83
Median	72.82	35.92	52.79
Min : Max	15.62 : 342.20	2.09 : 122.43	2.09 : 342.20
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	679.95	680.15	680.05
SD	494.62	350.26	408.62
Median	450.28	644.38	544.25
Min : Max	259.50 : 1427.5	267.66 : 1310.6	259.50 : 1427.5
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	374.07	489.86	431.97
SD	192.91	169.59	183.43
Median	398.19	552.75	520.20
Min : Max	96.60 : 565.80	176.40 : 618.84	96.60 : 618.84
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	75.99	58.26	67.12
SD	79.59	40.10	60.80
Median	52.84	59.93	59.93
Min : Max	19.44 : 229.95	11.60 : 125.28	11.60 : 229.95
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	59.11	55.90	57.50
SD	34.84	35.43	33.54
Median	58.93	43.50	51.62
Min : Max	13.65 : 106.08	17.70 : 115.20	13.65 : 115.20

Table 88 : Urine - Acetyl-L-carnitine [µmol] - Patients with a complete treatment

	Group A	Group B	All
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	46.50	16.76	31.63
SD	63.73	16.21	46.97
Median	15.60	14.83	15.60
Min : Max	5.13 : 167.40	0.94 : 43.68	0.94 : 167.40
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	224.98	278.06	251.52
SD	155.34	133.17	140.70
Median	187.06	267.58	238.48
Min : Max	89.85 : 490.00	82.86 : 457.70	82.86 : 490.00
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	143.67	178.23	160.95
SD	77.17	68.43	71.84
Median	187.05	188.22	187.05
Min : Max	20.40 : 199.54	69.35 : 253.75	20.40 : 253.75
Visit 4 (day 42)			
no. pts.	6	6	12
Mean	23.81	21.78	22.79
SD	20.94	13.23	16.73
Median	15.09	24.31	19.98
Min : Max	5.52 : 61.25	5.00 : 41.76	5.00 : 61.25
Visit 5 (day 56)			
no. pts.	6	6	12
Mean	21.00	35.02	28.01
SD	13.17	41.85	30.47
Median	20.72	18.53	20.72
Min : Max	4.55 : 42.90	7.15 : 118.80	4.55 : 118.80

Table 89 : Dyalisate - L-carnitine [µmol] - Patients with a complete treatment

	Group A
BASELINE visit (day 0)	
no. pts.	6
Mean	108.20
SD	46.96
Median	102.28
Min : Max	51.98 : 179.17
Visit 2 (day 14)	
no. pts.	6
Mean	703.63
SD	430.93
Median	861.96
Min : Max	138.69 : 1235.1
Visit 3 (day 28)	
no. pts.	6
Mean	246.47
SD	73.28
Median	223.96
Min : Max	154.56 : 339.94
Visit 4 (day 42)	
no. pts.	6
Mean	111.57
SD	34.79
Median	102.77
Min : Max	81.60 : 172.26
Visit 5 (day 56)	
no. pts.	6
Mean	108.52
SD	21.08
Median	106.33
Min : Max	86.02 : 136.76

Table 90 : Dyalisate - Acetyl-L-carnitine [µmol] - Patients with a complete treatment

	Group A
BASELINE visit (day 0)	
no. pts.	6
Mean	15.04
SD	8.16
Median	12.30
Min : Max	6.08 : 26.91
Visit 2 (day 14)	
no. pts.	6
Mean	31.82
SD	14.08
Median	30.23
Min : Max	17.78 : 50.82
Visit 3 (day 28)	
no. pts.	6
Mean	45.20
SD	20.47
Median	45.10
Min : Max	23.10 : 74.98
Visit 4 (day 42)	
no. pts.	6
Mean	16.99
SD	8.81
Median	15.78
Min : Max	5.29 : 32.48
Visit 5 (day 56)	
no. pts.	6
Mean	15.09
SD	3.27
Median	13.18
Min : Max	12.72 : 19.76

Table 91 : Oxalate [µmol/l] - Patients with a complete treatment

	Group A	Group B	All
BASELINE visit (day 0)			
no. pts.	6	6	12
Mean	95.75	70.23	82.99
SD	51.95	25.66	41.27
Median	72.78	69.23	72.73
Min : Max	62.19 : 198.19	37.86 : 110.97	37.86 : 198.19
Visit 2 (day 14)			
no. pts.	6	6	12
Mean	115.63	72.20	93.92
SD	69.80	22.00	54.30
Median	88.73	75.79	82.39
Min : Max	62.58 : 245.97	36.81 : 91.97	36.81 : 245.97
Visit 3 (day 28)			
no. pts.	6	6	12
Mean	93.01	79.62	86.31
SD	44.98	21.25	34.26
Median	91.17	75.24	77.71
Min : Max	36.97 : 167.14	53.08 : 116.75	36.97 : 167.14
Visit 4 (day 42)*			
no. pts.	5	6	11
Mean	105.77	84.47	94.15
SD	44.67	13.98	31.93
Median	107.25	82.39	85.81
Min : Max	48.58 : 159.92	70.61 : 107.08	48.58 : 159.92
Visit 5 (day 56)*			
no. pts.	5	6	11
Mean	85.02	45.72	63.58
SD	23.09	25.79	31.09
Median	83.25	47.09	59.00
Min : Max	51.81 : 113.03	14.42 : 83.72	14.42 : 113.03

*) 1 patient with missing data at Visit 4 (Day 42) and Visit 5 (Day 56)

Table 92: L-carnitine – Correlations between different samples (Serum-Urine-Dyalisate)

Visit Day 28 (T28)

Pearson Correlation Coefficient *p-value*	Urine (n=12)	Dyalisate (n=6)
Serum (n=12)	0.55 N.S.	0.94 0.004
Urine (n=12)	/	0.67 N.S.

N.S.: Not statistically significant

Visit Day 56 (T56)

Pearson Correlation Coefficient *p-value*	Urine (n=12)	Dyalisate (n=6)
Serum (n=12)	0.62 0.02	0.59 N.S.
Urine (n=12)	/	0.01 N.S.

N.S.: Not statistically significant

Table 93: Acetyl-L-carnitine – Correlations between different samples (Serum-Urine-Dyalisate)

Visit Day 28 (T28)

Pearson Correlation Coefficient *p-value*	Urine (n=12)	Dyalisate (n=6)
Serum (n=12)	0.44 N.S.	0.98 0.0003
Urine (n=12)	/	0.67 N.S.

N.S.: Not statistically significant

Visit Day 56 (T56)

Pearson Correlation Coefficient *p-value*	Urine (n=12)	Dyalisate (n=6)
Serum (n=12)	-0.21 N.S.	-0.72 N.S.
Urine (n=12)	/	-0.49 N.S.

N.S.: Not statistically significant

Appendix 1: Efficacy analysis

Study **IP-001-09**

Efficacy and safety assessments of a peritoneal dialysis solution containing Glucose, Xylitol and L-Carnitine compared to standard PD solutions in Continuous Ambulatory Peritoneal Dialysis (CAPD)

Statistical analysis (exploratory) – Efficacy parameters

Date: 07/09/2023

Version: final

Commento ai risultati:

Considerato che lo scopo di queste analisi è prettamente esplorativo e che il numero di pazienti coinvolti è largamente al di sotto del numero previsto nel protocollo di studio, l'analisi è stata condotta con approccio "non parametrico", utilizzando il test "Wilcoxon Matched-Pairs Signed-Ranks test" e senza alcuna correzione del "p-value" per confronti multipli.

Per quanto riguarda il confronto fra le singole visite Day-0 (Visita 1), Day-28 (Visita 2) e Day-56 (Visita 3), i risultati sono riassunti nelle Tabelle numerate da 1 a 4 e i risultati dell'analisi sono stati i seguenti:

Weekly Total Urea Kt/V (Tables 1): nessuna differenza statisticamente significativa è stata evidenziata per la variazione dei valori fra Visita 1 e Visita 2 (delta = 0.106 ± 0.239; Table 1.1), fra Visita 1 e Visita 3 (delta = 0.058 ± 0.340; Table 1.2), e fra Visita 2 e Visita 3 (delta = -0.049 ± 0.219; Table 1.3).

Peritoneal Equilibration Test/PET - Dialysate/Plasma creatinine (Tables 2.1-.2-.3): nessuna differenza statisticamente significativa è stata evidenziata per la variazione dei valori sia fra Visita 1 e Visita 3 (delta = 0.051 ± 0.157; Table 2.2) che fra Visita 2 e Visita 3 (delta = -0.025 ± 0.057; Table 2.3), mentre, al contrario, l'analisi è stata in grado di evidenziare una differenza statisticamente significativa per la variazione dei valori fra Visita 1 (Day-0: 0.573 ± 0.130) e Visita 2 (Day-28: 0.643 ± 0.058) (Table 2.1: delta = 0.070 ± 0.148; p = 0.0322).

Peritoneal Equilibration Test/PET - Glucose (Tables 2.4-.5-.6): nessuna differenza statisticamente significativa per la variazione dei valori fra le diverse visite; da notare comunque che la variazione fra Visita 1 e Visita 3 (Table 2.5: 0.050 ± 0.089) "mostri una tendenza" alla significatività (p = 0.0547).

Weekly Total Creatinine Clearance: nessuna differenza statisticamente significativa è stata evidenziata per la variazione dei valori fra Visita 1 e Visita 2 (delta = 2.71 ± 12.09; Table 3.1), fra Visita 1 e Visita 3 (delta =
-1.11 ± 13.17; Table 3.2), e fra Visita 2 e Visita 3 (delta = -4.25 ± 11.42; Table 3.3).

Total ultrafiltration: nessuna differenza statisticamente significativa per quanto riguarda la variazione dei valori fra Visita 1 e Visita 2 (delta = 37.50 ± 128.14; Table 4.1). Per quanto riguarda invece la differenza fra Visita 1 (Day-0: 316.67 ± 271.64) e Visita 3 (Day-56: 483.33 ± 289.46), l'analisi ha evidenziato una differenza statisticamente significativa (Table 4.2; delta = 166.67 ± 154.23; p = 0.0039). Inoltre, per quanto riguarda la differenza fra Visita 2 (Day-28: 354.17 ± 264.11) e Visita 3 (Day-56: 483.33 ± 289.46) l'analisi ha evidenziato una differenza statisticamente significativa ((Table 4.3; delta = 129.17 ± 143.75; p = 0.0117).

Per quanto riguarda il confronto fra i due periodi di trattamento (Periodo 1: “Intervention Period” e Periodo 2: “Follow up Period”), sono stati confrontate, rispettivamente, le variazioni Day 0-Day 28 e Day 28-Day 56, e i risultati sono riassunti nelle Tabelle numerate da 5 a 8.

I risultati dell’analisi sono stati i seguenti:

Weekly Total Urea Kt/V (Table 5): nessuna differenza statisticamente significativa è stataevidenziata fra i due periodi di trattamento (changes (Period 1 vs Period 2) = -0.156 ± 0.325; p = 0.11).

Peritoneal Equilibration Test/PET - Dialysate/Plasma creatinine (Table 6.1): vi è stata una diminuzione dei valori di PET rilevati nel Periodo 2 rispetto a quelli nel Periodo 1 (changes (Period 1 vs Period 2) = -0.102 ± 0.170) e tale diminuzione è risultata statisticamente significativa (p = 0.0225).

Peritoneal Equilibration Test/PET - Glucose (Table 6.2): nessuna differenza statisticamente significativa (p=071) fra i due periodi di trattamento (changes (Period 1 vs Period 2) = -0.024 ± 0.150; p=0.71)

Weekly Total Creatinine Clearance (Table 7): è stata rilevata una diminuzione dei valori del Periodo 2 rispetto a quelli del Periodo 1 (changes (Period 1 vs Period 2) = -7.39 ± 20.10) ma tale differenza è risultata statisticamente non significativa (p=0.46).

Total ultrafiltration (Table 8): nessuna differenza statisticamente significativa fra i due periodi di trattamento (changes (Period 1 vs Period 2) = 91.67 ± 224.45; p=0.24)

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Table 1.1: Weekly Total Urea Kt/V - Changes (day 28-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	12	1.307	0.253	0.073	0.760	1.300	1.680
Visit 2 (day 28)	12	1.413	0.230	0.066	1.070	1.445	1.750
Changes (day 28-day 0)	12	0.106	0.239	0.069	-0.160	0.070	0.760

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.1694

Table 1.2: Weekly Total Urea Kt/V - Changes (day 56-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	11	1.316	0.263	0.079	0.760	1.360	1.680
Visit 3 (day 56)	11	1.375	0.244	0.074	1.060	1.350	1.840
Changes (day 56-day 0)	11	0.058	0.340	0.102	-0.380	-0.040	0.820

Changes (day 56-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.7646

Table 1.3: Weekly Total Urea Kt/V - Changes (day 56-day 28)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 2 (day 28)	11	1.424	0.238	0.072	1.070	1.470	1.750
Visit 3 (day 56)	11	1.375	0.244	0.074	1.060	1.350	1.840
Changes (day 56-day 28)	11	-0.049	0.219	0.066	-0.430	-0.010	0.420

Changes (day 56-day 28) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.3613

Table 2.1: Peritoneal Equilibration Test (PET) - Dialysate/Plasma creatinine - Changes (day 28-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	12	0.573	0.130	0.037	0.220	0.600	0.710
Visit 2 (day 28)	12	0.643	0.058	0.017	0.560	0.635	0.740
Changes (day 28-day 0)	12	0.070	0.148	0.043	-0.120	0.040	0.500

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.0322

Table 2.2: Peritoneal Equilibration Test (PET) - Dialysate/Plasma creatinine - Changes (day 56-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	11	0.561	0.128	0.039	0.220	0.590	0.710
Visit 3 (day 56)	11	0.612	0.074	0.022	0.510	0.620	0.700
Changes (day 56-day 0)	11	0.051	0.157	0.047	-0.100	0.040	0.480

Changes (day 56-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.5156

Table 2.3: Peritoneal Equilibration Test (PET) - Dialysate/Plasma creatinine - Changes (day 56-day 28)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 2 (day 28)	11	0.637	0.056	0.017	0.560	0.630	0.740
Visit 3 (day 56)	11	0.612	0.074	0.022	0.510	0.620	0.700
Changes (day 56-day 28)	11	-0.025	0.057	0.017	-0.150	-0.020	0.040

Changes (day 56-day 28) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.2676

Table 2.4: Peritoneal Equilibration Test (PET) - Glucose - Changes (day 28-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	10	0.245	0.098	0.031	0.000	0.270	0.340
Visit 2 (day 28)	10	0.282	0.038	0.012	0.220	0.280	0.340
Changes (day 28-day 0)	10	0.037	0.103	0.032	-0.050	0.015	0.310

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.2695

Table 2.5: Peritoneal Equilibration Test (PET) - Glucose - Changes (day 56-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	10	0.245	0.098	0.031	0.000	0.270	0.340
Visit 3 (day 56)	10	0.295	0.065	0.021	0.220	0.280	0.420
Changes (day 56-day 0)	10	0.050	0.089	0.028	-0.030	0.045	0.270

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.0547

Table 2.6: Peritoneal Equilibration Test (PET) - Glucose - Changes (day 56-day 28)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 2 (day 28)	10	0.282	0.038	0.012	0.220	0.280	0.340
Visit 3 (day 56)	10	0.295	0.065	0.021	0.220	0.280	0.420
Changes (day 56-day 28)	10	0.013	0.069	0.022	-0.080	0.005	0.150

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.6563

Table 3.1: Weekly Total Creatinine Clearance - Changes (day 28-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	12	68.38	16.20	4.68	43.28	67.42	93.39
Visit 2 (day 28)	12	71.09	21.33	6.16	42.38	67.85	105.74
Changes (day 28-day 0)	12	2.71	12.09	3.49	-22.59	2.36	24.79

Changes (day 28-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.3394

Table 3.2: Weekly Total Creatinine Clearance - Changes (day 56-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	11	69.70	16.30	4.91	43.28	72.22	93.39
Visit 3 (day 56)	11	68.59	20.44	6.16	42.60	65.26	112.38
Changes (day 56-day 0)	11	-1.11	13.17	3.97	-19.70	-1.86	26.86

Changes (day 56-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.5771

Table 3.3: Weekly Total Creatinine Clearance - Changes (day 56-day 28)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 2 (day 28)	11	72.84	21.45	6.47	42.38	69.88	105.74
Visit 3 (day 56)	11	68.59	20.44	6.16	42.60	65.26	112.38
Changes (day 56-day 28)	11	-4.25	11.42	3.44	-21.49	0.14	16.60

Changes (day 56-day 28) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.5195

Table 4.1: Total ultrafiltration (mL) - Changes (day 28-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	12	316.67	271.64	78.42	0.00	300.00	1050.00
Visit 2 (day 28)	12	354.17	264.11	76.24	100.00	300.00	1000.00
Changes (day 28-day 0)	12	37.50	128.14	36.99	-100.00	0.00	350.00

Changes (day 56-day 28) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.5000

Table 4.2: Total ultrafiltration (mL) - Changes (day 56-day 0)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 1 (day 0)	12	316.67	271.64	78.42	0.00	300.00	1050.00
Visit 3 (day 56)	12	483.33	289.46	83.56	0.00	425.00	1150.00
Changes (day 56-day 0)	12	166.67	154.23	44.52	0.00	150.00	400.00

Changes (day 56-day 0) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.0039

Table 4.3: Total ultrafiltration (mL) - Changes (day 56-day 28)

Visit	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Visit 2 (day 28)	12	354.17	264.11	76.24	100.00	300.00	1000.00
Visit 3 (day 56)	12	483.33	289.46	83.56	0.00	425.00	1150.00
Changes (day 56-day 28)	12	129.17	143.75	41.50	-100.00	150.00	400.00

Changes (day 56-day 28) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.0117

Table 5: Weekly Total Urea Kt/V - Comparison BETWEEN Periods (WITHIN patients)

Study Period	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Intervention Period - delta day 0-28	11	0.107	0.251	0.076	-0.160	0.050	0.760
Follow up Period - delta day 28-56	11	-0.049	0.219	0.066	-0.430	-0.010	0.420
Changes (Intervention vs Follow up)	11	-0.156	0.325	0.098	-0.700	-0.230	0.430

Changes (Period 1 vs Period 2) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.1162

Table 6.1: Peritoneal Equilibratione Test (PET) - Dialysate/Plasma creatinine - Comparison BETWEEN Periods (WITHIN patients)

Study Period	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Intervention Period - delta day 0-28	11	0.076	0.153	0.046	-0.120	0.050	0.500
Follow up Period - delta day 28-56	11	-0.025	0.057	0.017	-0.150	-0.020	0.040
Changes (Intervention vs Follow up)	11	-0.102	0.170	0.051	-0.520	-0.060	0.150

Changes (Period 1 vs Period 2)- Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.0225

Table 6.2: Peritoneal Equilibratione Test (PET) - Glucose - Comparison BETWEEN Periods (WITHIN patients)

Study Period	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Intervention Period - delta day 0-28	10	0.037	0.103	0.032	-0.050	0.015	0.310
Follow up Period - delta day 28-56	10	0.013	0.069	0.022	-0.080	0.005	0.150
Changes (Intervention vs Follow up)	10	-0.024	0.150	0.048	-0.350	-0.010	0.200

Changes (Period 1 vs Period 2)- Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.7129

Table 7: Weekly Total Creatinine Clearance - Comparison BETWEEN Periods (WITHIN patients)

Study Period	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Intervention Period - delta day 0-28	11	3.14	12.58	3.79	-22.59	2.94	24.79
Follow up Period - delta day 28-56	11	-4.25	11.42	3.44	-21.49	0.14	16.60
Changes (Intervention vs Follow up)	11	-7.39	20.10	6.06	-39.78	-6.19	26.80

Changes (Period 1 vs Period 2) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.4648

Table 8: Total ultrafiltration (mL) - Comparison BETWEEN Periods (WITHIN patients)

Study Period	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
Intervention Period - delta day 0-28	12	37.50	128.14	36.99	-100.00	0.00	350.00
Follow up Period - delta day 28-56	12	129.17	143.75	41.50	-100.00	150.00	400.00
Changes (Intervention vs Follow up)	12	91.67	224.45	64.79	-300.00	100.00	500.00

Changes (Period 1 vs Period 2) - Wilcoxon Matched-Pairs Signed-Ranks test: p = 0.2422

Appendix 2: Safety parameters - Evaluation - Clinically significant values

Table 1: Safety parameters - Evaluation - Clinically significant values

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Clinical parameters - Blood Pressure and Heart Rate – Evaluation

- All parameters were assessed as “Normal” or “Not Clinically Significant” between Day 0 and Day 56

Haematology – Evaluation - Clinically significant values

- All parameters were assessed as “Normal” or “Not Clinically Significant” between Day 0 and Day 56

Biochemistry – Evaluation - Clinically significant values

- All parameters were assessed as “Normal” or “Not Clinically Significant” between Day 0 and Day 56

ECG – evaluation - Evaluation - Clinically significant values

Patient no.	Visit no.	ECG normal	ECG abnormality	ECG evaluation
01-001	Day 0	No	Sinus Bradycardia	Clinically significant for concomitant disease
	Day 28	No	Sinus Bradycardia	Clinically sign. for the pathology under study
01-005	Day 0	No	Sinus Bradycardia	Clinically significant for concomitant disease
	Day 28	Yes	.	.

01-006	Day 0	No	Sinus Bradycardia	Clinically significant for concomitant disease
	Day 28	No	Right Bundle Branch Block	Clinically significant for concomitant disease
01-007	Day 0	No	Left Bundle Branch Block	Clinically significant for concomitant disease
	Day 28	No	Left Bundle Branch Block	Clinically significant for concomitant disease
01-009	Day 0	No	Other: Sinus rhythm, previous lower myocardial infarction	Clinically significant for concomitant disease
	Day 28	Yes	.	.

Study **IP-001-09**

Efficacy and safety assessments of a peritoneal dialysis solution containing Glucose, Xylitol and L-Carnitine compared to standard PD solutions in Continuous Ambulatory Peritoneal Dialysis (CAPD)

Statistical analysis – Listings

Date: 07/09/2023

Version: final

Author: Antonio Colantoni

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Listing 1.1 - Study IP-001-09 : Disposition of patients

Site no.	Patient no.	Screened	Pat. eligible	Randomized	Treatment no.	Treatment group	Study completed	Treatment completed	Principal Reason for Subject Premature discontinuation
1	01-001	Yes	Yes	Yes	1	B	Yes	Yes	
1	01-002	Yes	Yes	Yes	2	B	Yes	Yes	
1	01-003	Yes	Yes	Yes	3	B	Yes	Yes	
1	01-004	Yes	Yes	Yes	4	A	Yes	Yes	
1	01-005	Yes	Yes	Yes	5	A	Yes	Yes	
1	01-006	Yes	Yes	Yes	6	A	Yes	Yes	
1	01-007	Yes	Yes	Yes	7	A	Yes	Yes	
1	01-008	Yes	Yes	Yes	8	B	Yes	Yes	
1	01-009	Yes	Yes	Yes	9	A	Yes	Yes	
1	01-010	Yes	Yes	Yes	10	A	No	No	Lost to follow up
1	01-011	Yes	Yes	Yes	11	A	Yes	Yes	
5	05-001	Yes	Yes	Yes	1	B	Yes	Yes	
5	05-002	Yes	Yes	Yes	2	B	Yes	Yes	
6	06-001	Yes		No	.	.	No	No	Inclusion/Exclusion criteria not fulfilled
6	06-002	Yes		No	.	.	No	No	Inclusion/Exclusion criteria not fulfilled

Listing 1.2 - Study IP-001-09 : Disposition of patients - Reason for discontinuation - details

Site no.	Patient no.	Principal Reason for Subject Premature discontinuation - details
6	06-001	the patient has been treated with 2.5% glucose solution bags
6	06-002	the patient has been treated with 2.5% glucose solution bags

Listing 1.3 - Study IP-001-09 : Visits dates (dd/mm/yy)

Patient no.	Informed consent	Screening Day -28	Day 0	Day 14	Day 28	Day 42	Day 56	Date of last visit	Date of last treatment
01-001	16/10/2019	16/10/2019	13/11/2019	28/11/2019	12/12/2019	23/12/2019	07/01/2020	07/01/2020	.
01-002	13/11/2019	13/11/2019	11/12/2019	27/12/2019	08/01/2020	22/01/2020	05/02/2020	05/02/2020	.
01-003	13/11/2019	13/11/2019	11/12/2019	27/12/2019	10/01/2020	22/01/2020	05/02/2020	05/02/2020	.
01-004	15/11/2019	15/11/2019	13/12/2019	27/12/2019	09/01/2020	23/01/2020	10/02/2020	10/02/2020	.
01-005	15/11/2019	15/11/2019	13/12/2019	27/12/2019	10/01/2020	24/01/2020	07/02/2020	07/02/2020	.
01-006	20/11/2019	20/11/2019	18/12/2019	03/01/2020	15/01/2020	29/01/2020	12/02/2020	12/02/2020	.
01-007	21/11/2019	21/11/2019	19/12/2019	03/01/2020	16/01/2020	30/01/2020	13/02/2020	13/02/2020	.
01-008	21/11/2019	21/11/2019	19/12/2019	03/01/2020	16/01/2020	30/01/2020	13/02/2020	13/02/2020	.
01-009	26/11/2019	26/11/2019	23/12/2019	07/01/2020	21/01/2020	04/02/2020	18/02/2020	18/02/2020	.
01-010	10/12/2019	10/12/2019	08/01/2020	.	.	.	.	22/01/2020	22/01/2020
01-011	06/02/2020	06/02/2020	05/03/2020	20/03/2020	02/04/2020	16/04/2020	30/04/2020	30/04/2020	.
05-001	13/10/2021	13/10/2021	10/11/2021	26/11/2021	09/12/2021	28/12/2021	22/02/2022	22/02/2022	.
05-002	29/10/2021	29/10/2021	30/11/2021	14/12/2021	30/12/2021	15/01/2022	03/02/2022	03/02/2022	.
06-001	15/12/2021	15/12/2021	.	.	.	.	.	15/12/2021	15/12/2021
06-002	15/12/2021	15/12/2021	.	.	.	.	.	15/12/2021	15/12/2021

Listing 1.4 - Study IP-001-09 : Inclusion criteria

Patient no.	I.C.#1	I.C.#2	I.C.#3	I.C.#4	I.C.#5	I.C.#6	I.C.#7	I.C.#8
01-001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
01-002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
01-003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
01-004	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-005	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-006	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-007	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
01-009	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-010	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-011	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
05-001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
05-002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
06-001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
06-002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Listing 1.5 - Study IP-001-09 : Exclusion criteria

Patient no.	E.C.#1	E.C.#2	E.C.#3	E.C.#4	E.C.#5	E.C.#6	E.C.#7	E.C.#8	E.C.#9	E.C.#10	E.C.#11	E.C.#12
01-001	No	No	No	No	No	No	No	No	Na	No	No	No
01-002	No	No	No	No	No	No	No	No	Na	No	No	No
01-003	No	No	No	No	No	No	No	No	Na	No	No	No
01-004	No	No	No	No	No	No	No	No	Na	No	No	No
01-005	No	No	No	No	No	No	No	No	Na	No	No	No
01-006	No	No	No	No	No	No	No	No	Na	No	No	No
01-007	No	No	No	No	No	No	No	No	Na	No	No	No
01-008	No	No	No	No	No	No	No	No	Na	No	No	No
01-009	No	No	No	No	No	No	No	No	No	No	No	No
01-010	No	No	No	No	No	No	No	No	Na	No	No	No
01-011	No	No	No	No	No	No	No	No	No	No	No	No
05-001	No	No	No	No	No	No	No	No	Na	No	No	No
05-002	No	No	No	No	No	No	No	No	Na	No	No	No
06-001	No	No	No	No	No	No	No	No	Na	No	No	No
06-002	No	No	No	No	No	No	No	No	Na	No	No	No

Listing 2.1 - Study IP-001-09 : Demographic data

Patient no.	Type of patient	Sex	Date of birth (dd/mm/yy)	Age (yrs)	Race	Height (cm)	Weight (kg)	Significant medical/surgery history	Any treatment in the last 3 months	Physical Examination performed?	Physical Examination abnormalities	Pregnancy test (PT) done
01-001	Outpatient patient	Male	19/05/1956	63	White	175	82.0	Yes	Yes	Yes	Yes	
01-002	Outpatient patient	Male	12/01/1957	62	White	186	100.0	Yes	Yes	Yes	No	
01-003	Outpatient patient	Male	02/07/1982	37	White	172	90.5	Yes	Yes	Yes	No	
01-004	Outpatient patient	Female	31/10/1944	75	White	162	66.0	Yes	Yes	Yes	No	Na
01-005	Outpatient patient	Male	22/05/1952	67	White	165	98.0	Yes	Yes	Yes	No	
01-006	Outpatient patient	Male	15/11/1949	70	White	170	80.0	Yes	Yes	Yes	No	
01-007	Outpatient patient	Male	16/03/1959	60	White	175	72.0	Yes	Yes	Yes	No	
01-008	Outpatient patient	Male	09/06/1960	59	White	175	86.0	Yes	Yes	Yes	No	
01-009	Outpatient patient	Female	28/04/1947	72	White	165	93.0	Yes	Yes	Yes	No	Na
01-010	Outpatient patient	Male	13/07/1952	67	White	175	91.0	Yes	Yes	Yes	No	
01-011	Outpatient patient	Female	30/09/1946	73	White	155	51.0	Yes	Yes	Yes	No	Na
05-001	Outpatient patient	Male	04/06/1939	82	White	160	64.2	Yes	Yes	Yes	No	
05-002	Outpatient patient	Male	05/07/1942	79	White	169	66.0	Yes	Yes	Yes	No	
06-001	Outpatient patient	Male	29/04/1935	86	White	168	74.5	Yes	Yes	Yes	No	
06-002	Outpatient patient	Male	29/07/1946	75	White	167	68.7	Yes	Yes	Yes	No	

Listing 2.2 - Study IP-001-09 : Medical and Surgical history (MH)

Patient no.	MH no.	Disease/Surgery	Date of Diagnosis (dd/mm/yy)	Date of Resolution (dd/mm/yy)	Ongoing
01-001	1	Lung tumor	na/07/2018	12/07/2018	No
	2	GERD	na/na/2010		Yes
	3	Tonsillectomy	na/na/1966	na/na/1966	No
	5	Lobectomy	12/07/2018	12/07/2018	No
	6	Peritoneal catheter positioning	na/04/2019	na/04/2019	No
	7	hypertension	na/na/1999		Yes
	8	hypercholesterolemia	na/na/2017		Yes
	9	hyperuricemia	na/na/2017		Yes
01-002	1	Heart attack	na/na/2007	na/na/2007	No
	2	Diabetes mellitus tipe II	na/na/2010		Yes
	3	Chronic lymphatic leukemia	na/na/2013		Yes
	4	Appendectomy	na/na/1975	na/na/1975	No
	5	Left nephrectomy for kidney cancer	na/na/2002	na/na/2002	No
	6	Peritoneal catheter positioning	10/05/2019		Yes
	7	hyperuricemia	na/na/2018		Yes
	8	hypertension	na/na/2010		Yes
	9	hypercholesterolemia	na/na/2015		Yes
01-003	1	Ureteral bladder reflux	na/na/2001		Yes
	2	Pyelonephritis	na/na/2002	na/na/2002	No
	3	Ureteral reimplantation intervention	na/06/2018	na/06/2018	No
	4	Tonsillectomy	na/na/1995	na/na/1995	No
	5	hyperuricemia	na/na/2018		Yes
	6	Benign prostatic hypertrophy	na/na/2005		Yes
	7	Positioning Peritoneal catheter	na/05/2019		Yes
	8	Penicilline and cefalosporine allergy	na/na/na		Yes
	9	Anemia	11/12/2019		Yes
01-004	1	Hypertension	na/na/2000		Yes
	2	Pericarditis	na/na/2005	na/na/2005	No
	3	Parathyroidectomy	na/na/2001	na/na/2001	No
	4	GERD	na/na/2010		Yes
	5	Peritoneal catheter positioning	na/06/2019		Yes
	6	hypercholesterolemia	na/na/2017		Yes
	7	hyperuricemia	na/na/2019		Yes
	8	Appendectomy	na/na/na/	na/na/na	No
	9	Anemia	na/09/2019		Yes

Listing 2.2 - Study IP-001-09 : Medical and Surgical history (MH)

Patient no.	MH no.	Disease/Surgery	Date of Diagnosis (dd/mm/yy)	Date of Resolution (dd/mm/yy)	Ongoing
01-005	1	hypertension	na/na/2002		Yes
	2	hyperuricemia	na/na/2017		Yes
	3	hypercholesterolemia	na/na/2003		Yes
	4	knee prosthesis implant	na/na/2011	na/na/2011	No
	5	peritoneal catheter positioning	na/06/2019		Yes
	6	diabetes mellitus tipe 2	na/na/2005		Yes
	7	cardioaspirin allergy	na/na/na		Yes
	8	Anemia	na/08/2019		Yes
01-006	1	Hypertension	na/na/1980		Yes
	2	Hypothyroidism	na/na/2005		Yes
	3	Peritoneal catheter positioning	na/03/2019		Yes
	4	Left hernioplastic	na/na/2018	na/na/2018	No
	5	Hyperuricemia	na/na/2019		Yes
	6	Anemia	na/na/2019		Yes
01-007	1	Acute myocardial infarction	na/03/2015	na/03/2015	No
	2	Coronary artery angioplasty	na/03/2015	na/03/2015	No
	3	Diabetes mellitus tipe II	na/na/2005	na/na/2012	No
	4	Peritoneal catheter positioning	na/07/2019		Yes
	5	Hypertension	na/na/2015		Yes
	6	Dysplipidemia	na/na/2015		Yes
	7	Hyperuricemia	na/na/2015		Yes
	8	Anxious syndrome	na/na/2010		Yes
	9	allergy to rocefin	na/na/na		Yes
	10	Anemia	na/na/2015		Yes
	12	Chronic Kidney Disease- associated pruritus (CKD- aP)	03/01/2020		Yes
01-008	1	Infarction myocardial	na/na/2005	na/na/2005	No
	2	Coronary angioplasty	na/na/2005	na/na/2005	No
	3	Peritoneal catheter positioning	na/04/2019		Yes
	5	hypertension	na/na/2018		Yes
	6	Anemia	na/na/2019		Yes
	7	Hyperuricemia	na/na/na		Yes
01-009	1	Mild aortic insufficiency	na/na/1980		Yes
	2	Ascending aorta ectasia	na/na/2017		Yes
	3	Hypertension	na/na/1980		Yes
	4	Varicose veins lower limbs	na/na/2000		Yes

Listing 2.2 - Study IP-001-09 : Medical and Surgical history (MH)

Patient no.	MH no.	Disease/Surgery	Date of Diagnosis (dd/mm/yy)	Date of Resolution (dd/mm/yy)	Ongoing
01-009	5	Type B gastritis	na/na/2017		Yes
	6	Hysteroannessiectomy	na/na/2000	na/na/2000	No
	7	Hypothyroidism	na/na/2012		Yes
	8	Appendectomy	na/na/1961	na/na/1961	No
	9	Tonsillectomy	na/na/1963	na/na/1963	No
	10	Umbilical hernia correction	na/na/2015	na/na/2015	No
	11	peritoneal catheter positioning	na/04/2019		Yes
	12	Anemia	na/na/2019		Yes
01-010	1	Aortic insufficiency	na/03/2017		Yes
	3	Hypertension	na/na/2010		Yes
	4	Prostatic hypertrophy	na/na/2017	na/na/2017	No
	5	TURB	na/na/2017	na/na/2017	No
	6	Appendectomy	na/na/1972	na/na/1972	No
	7	Peritoneal catheter positioning	na/07/2019		Yes
	8	Hyperuricemia	na/na/2017		Yes
	9	anemia	na/na/2019		Yes
01-011	1	Hypertension	na/na/2010		Yes
	2	Peritoneal catheter positioning	na/03/2019		Yes
	3	Tonsillectomy	na/na/1954	na/na/1954	No
	4	Radical left mastectomy	na/na/2009	na/na/2009	No
	5	Hyperuricemia	na/na/2017		Yes
	6	anemia	na/na/2019		Yes
05-001	1	Osteoporosis	na/na/na		Yes
	2	Bilateral hip replacement	na/na/2017		Yes
	3	Atrial fibrillation	17/08/2020		Yes
	4	Cholecystectomy	na/na/2000		Yes
	5	Hypertension	na/na/na		Yes
	6	COPD	na/na/na		Yes
	7	prostatic hypertrophy	na/na/na		Yes
	8	Frequent bradycardia	na/na/na		Yes
05-002	1	BPH	na/na/1997	na/na/1998	No
	2	hypertension	na/na/1988		Yes
	3	diabetes mellitus type II	na/na/2000		Yes
	4	dyslipidemia	na/na/2000		Yes
	5	Crohn's disease	na/11/2020		Yes

Listing 2.2 - Study IP-001-09 : Medical and Surgical history (MH)

Patient no.	MH no.	Disease/Surgery	Date of Diagnosis (dd/mm/yy)	Date of Resolution (dd/mm/yy)	Ongoing
05-002	6	Nefroangiosclerosis	07/07/2017		Yes
06-001	1	peritoneal catheter insertion	06/11/2014		Yes
06-002	1	peritoneal catheter insertion	01/01/2016		Yes
	2	kydney transplant	05/11/2019	12/11/2019	No
	3	transplanted kidney explant	22/11/2019	22/11/2019	No
	4	covid relate infection	01/11/2020	15/11/2020	No

Listing 2.3 - Study IP-001-09 : Physical Examination (PE) - abnormalities

Patient no.	PE no.	Test	Result/Description
01-001	1	Other	RIGHT LOWER LIMB EDEMA

Listing 3 - Study IP-001-09 : Clinical parameters

Patient no.	Visit no.	Weight (kg)	Systolic BP (mmHg)	SBP evaluation	Diastolic BP (mmHg)	DBP evaluation	Heart Rate (beats/ min)	HR evaluation	Diuresis (L/day)	Hyperhydratation signs
01-001	Screening	82.0	155	2	95	2	75	2	2.00	No
	Day 0	84.0	140	1	95	2	56	2	2.10	No
	Day 14	82.0	150	2	95	2	53	2	2.00	No
	Day 28	84.0	130	1	80	1	48	2	2.00	No
	Day 42	84.5	155	2	100	2	56	2	2.00	No
	Day 56	83.0	160	2	100	2	56	2	1.80	No
01-002	Screening	100.0	145	2	90	2	65	1	2.50	No
	Day 0	98.0	150	2	80	1	86	1	2.20	No
	Day 14	100.0	145	2	70	1	63	1	2.50	No
	Day 28	98.0	140	1	80	1	82	1	2.50	No
	Day 42	98.0	150	2	70	1	60	1	2.50	No
	Day 56	99.0	155	2	80	1	60	1	2.10	No
01-003	Screening	90.5	130	1	80	1	100	2	1.00	No
	Day 0	88.0	110	1	70	1	90	1	2.10	No
	Day 14	87.0	146	2	80	1	96	1	2.30	No
	Day 28	84.0	105	1	60	1	60	1	1.80	No
	Day 42	88.0	120	1	70	1	85	1	1.80	No
	Day 56	88.0	135	1	70	1	68	1	2.00	No
01-004	Screening	66.0	170	2	80	2	74	1	1.75	No
	Day 0	65.0	145	2	95	2	75	1	1.25	No
	Day 14	65.0	170	2	80	2	79	1	1.50	No
	Day 28	64.0	140	2	90	2	85	1	1.10	No
	Day 42	65.0	150	2	90	2	90	1	1.20	No
	Day 56	64.0	140	2	70	1	96	1	1.10	No
01-005	Screening	98.0	160	2	80	2	63	1	1.50	No
	Day 0	95.0	150	2	80	1	55	2	1.10	No
	Day 14	94.0	130	1	55	2	61	1	1.50	No
	Day 28	90.0	135	1	75	1	70	1	1.50	No
	Day 42	91.0	130	1	60	1	63	1	1.20	No
	Day 56	93.0	140	2	70	1	63	1	1.60	No
01-006	Screening	80.0	125	1	70	1	56	2	2.00	No

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 3 - Study IP-001-09 : Clinical parameters

Patient no.	Visit no.	Weight (kg)	Systolic BP (mmHg)	SBP evaluation	Diastolic BP (mmHg)	DBP evaluation	Heart Rate (beats/ min)	HR evaluation	Diuresis (L/day)	Hyperhydratation signs
01-006	Day 0	78.5	110	1	70	1	50	2	1.60	No
	Day 14	81.0	150	2	90	2	60	1	2.00	No
	Day 28	80.0	150	2	80	1	54	2	1.50	No
	Day 42	81.0	115	1	65	2	64	1	1.75	No
	Day 56	79.5	140	1	85	1	50	2	1.50	No
01-007	Screening	72.0	150	2	90	2	69	1	2.00	No
	Day 0	70.5	165	2	80	1	73	1	2.00	No
	Day 14	73.0	150	2	80	1	65	1	2.00	No
	Day 28	71.5	150	2	90	2	68	1	2.30	No
	Day 42	71.0	130	1	60	1	65	1	1.80	No
	Day 56	71.0	110	1	70	1	72	1	1.75	No
01-008	Screening	86.0	150	2	100	2	70	1	2.00	No
	Day 0	86.0	140	1	80	1	75	1	1.75	No
	Day 14	88.0	128	1	80	1	96	1	1.80	No
	Day 28	87.5	150	2	95	2	85	1	1.80	No
	Day 42	88.0	140	1	80	1	98	1	2.00	No
	Day 56	87.0	110	1	70	1	84	1	1.65	No
01-009	Screening	93.0	150	2	80	1	55	1	2.00	No
	Day 0	97.0	115	1	80	1	67	1	2.70	No
	Day 14	97.0	120	1	70	1	64	1	2.50	No
	Day 28	96.5	105	1	75	1	69	1	2.00	No
	Day 42	95.0	160	2	75	1	65	1	2.50	No
	Day 56	94.5	120	1	75	1	55	2	2.60	No
01-010	Screening	91.0	150	2	70	1	68	1	2.00	No
	Day 0	91.0	160	2	80	1	72	1	2.00	No
	Day 14	.	.	.	.	.	.	.	.	
	Day 28	.	.	.	.	.	.	.	.	
	Day 42	.	.	.	.	.	.	.	.	
	Day 56	.	.	.	.	.	.	.	.	
01-011	Screening	51.0	140	1	80	1	60	1	2.00	No
	Day 0	53.0	120	1	85	2	67	1	1.10	No

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 3 - Study IP-001-09 : Clinical parameters

Patient no.	Visit no.	Weight (kg)	Systolic BP (mmHg)	SBP evaluation	Diastolic BP (mmHg)	DBP evaluation	Heart Rate (beats/ min)	HR evaluation	Diuresis (L/day)	Hyperhydratation signs
01-011	Day 14	50.5	150	2	80	1	51	2	1.20	No
	Day 28	49.0	130	1	70	1	53	2	1.10	No
	Day 42	50.0	150	2	70	1	55	2	1.10	No
	Day 56	51.0	145	2	85	2	70	1	1.40	No
05-001	Screening	64.2	140	1	80	1	70	1	1.40	No
	Day 0	63.4	120	1	80	1	77	1	1.00	No
	Day 14	62.7	130	1	70	1	80	1	1.50	No
	Day 28	62.7	135	1	90	1	85	1	1.60	No
	Day 42	64.5	130	1	90	1	81	1	1.25	No
	Day 56	68.4	150	1	90	1	87	1	1.30	No
05-002	Screening	66.0	140	1	80	1	71	1	0.50	No
	Day 0	67.5	130	1	65	1	75	1	0.55	No
	Day 14	67.0	130	1	70	1	75	1	0.60	No
	Day 28	69.0	135	1	80	1	70	1	0.50	Yes
	Day 42	68.0	140	1	75	1	77	1	0.40	No
	Day 56	68.5	140	1	80	1	70	1	0.50	No
06-001	Screening	74.5	145	1	78	1	67	1	1.10	No
06-002	Screening	68.7	125	1	70	1	59	1	1.60	No

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 4 - Study IP-001-09 : Ulrafiltration, CA 125 and Proteins

Patient no.	Visit no.	1st Daily Bag (mL)	2nd Daily Bag (mL)	3rd Daily Bag (mL)	Nocturnal Bag (mL)	Total ultrafiltration (mL)	CA 125 (U.a./ mL)	Proteins in ultrafiltration (mg/L)
01-001	Screening	-100	-150	0	750	500	23.6	2.2
	Day 0	100	100	0	200	400	54.6	2.2
	Day 14	100	100	0	100	300	62.0	2.2
	Day 28	100	100	0	100	300	145.9	0.8
	Day 42	100	100	0	100	300	.	.
	Day 56	150	100	0	200	450	110.9	0.8
01-002	Screening	100	0	0	400	500	22.8	2.2
	Day 0	150	0	0	250	400	45.5	0.8
	Day 14	150	0	0	250	400	59.8	.
	Day 28	150	0	0	250	400	66.7	0.8
	Day 42	150	0	0	350	500	.	.
	Day 56	150	0	0	250	400	76.8	0.8
01-003	Screening	100	100	0	200	400	60.8	2.2
	Day 0	100	50	0	150	300	.	0.8
	Day 14	50	100	0	150	300	51.8	0.8
	Day 28	50	100	0	150	300	73.7	0.8
	Day 42	50	50	0	200	300	.	.
	Day 56	100	100	0	100	300	104.4	0.8
01-004	Screening	-100	0	0	0	-100	58.3	2.2
	Day 0	0	0	0	0	0	81.0	0.8
	Day 14	100	0	0	0	100	68.0	0.8
	Day 28	200	0	0	0	200	67.9	0.8
	Day 42	200	0	0	0	200	.	.
	Day 56	400	0	0	0	400	52.9	0.8
01-005	Screening	200	0	0	0	200	54.6	2.2
	Day 0	0	0	0	0	0	42.9	0.8
	Day 14	100	0	0	0	100	56.4	0.8
	Day 28	100	0	0	0	100	75.4	0.8
	Day 42	0	0	0	0	0	.	.
	Day 56	0	0	0	0	0	76.4	0.8
01-006	Screening	0	0	0	0	0	29.9	2.2
	Day 0	100	0	0	0	100	52.6	0.8
	Day 14	250	0	0	0	250	45.3	0.8

Listing 4 - Study IP-001-09 : Ulrafiltration, CA 125 and Proteins

Patient no.	Visit no.	1st Daily Bag (mL)	2nd Daily Bag (mL)	3rd Daily Bag (mL)	Nocturnal Bag (mL)	Total ultrafiltration (mL)	CA 125 (U.a./ mL)	Proteins in ultrafiltration (mg/L)
01-006	Day 28	100	0	0	0	100	66.1	0.8
	Day 42	300	0	0	0	300	.	.
	Day 56	300	0	0	0	300	39.5	0.8
01-007	Screening	100	0	0	0	100	106.3	2.2
	Day 0	300	0	0	0	300	184.0	0.8
	Day 14	200	0	0	0	200	203.1	0.8
	Day 28	200	0	0	0	200	209.2	0.8
	Day 42	900	0	0	0	900	.	.
	Day 56	600	0	0	0	600	224.7	0.8
01-008	Screening	50	100	250	0	400	59.4	2.2
	Day 0	50	50	0	200	300	88.6	0.8
	Day 14	150	50	0	100	300	51.9	0.8
	Day 28	50	50	0	200	300	109.4	0.8
	Day 42	200	150	0	250	600	.	.
	Day 56	200	200	0	200	600	90.7	0.8
01-009	Screening	500	0	0	0	500	33.6	2.2
	Day 0	300	0	0	0	300	61.4	0.8
	Day 14	300	0	0	0	300	63.3	0.8
	Day 28	300	0	0	0	300	93.4	0.8
	Day 42	400	0	0	0	400	.	.
	Day 56	500	0	0	0	500	57.7	0.8
01-010	Screening	200	0	0	0	200	38.1	0.8
	Day 0	0	0	0	100	100	35.9	0.8
	Day 14	.	.	.	.	.	.	.
	Day 28	.	.	.	.	.	.	.
	Day 42	.	.	.	.	.	.	.
	Day 56	.	.	.	.	.	.	.
01-011	Screening	100	0	0	0	100	61.4	0.8
	Day 0	250	0	0	0	250	46.2	0.8
	Day 14	300	0	0	0	300	52.3	0.8
	Day 28	300	0	0	0	300	60.9	0.8
	Day 42	250	0	0	0	250	.	.
	Day 56	300	0	0	0	300	41.6	0.8

Listing 4 - Study IP-001-09 : Ulrafiltration, CA 125 and Proteins

Patient no.	Visit no.	1st Daily Bag (mL)	2nd Daily Bag (mL)	3rd Daily Bag (mL)	Nocturnal Bag (mL)	Total ultrafiltration (mL)	CA 125 (U.a./ mL)	Proteins in ultrafiltration (mg/L)
05-001	Screening	-50	-150	0	750	550	.	.
	Day 0	-200	-50	0	650	400	9.9	0.3
	Day 14	100	-100	0	700	700	10.9	0.3
	Day 28	100	-100	0	750	750	11.9	2.6
	Day 42	50	100	200	700	1050	.	.
	Day 56	100	150	50	500	800	10.7	0.3
05-002	Screening	150	150	0	1050	1350	23.2	2.0
	Day 0	100	-100	0	1050	1050	24.0	.
	Day 14	550	50	0	450	1050	25.1	0.0
	Day 28	1050	-1050	0	1000	1000	21.9	0.3
	Day 42	1100	0	300	100	1500	.	.
	Day 56	200	-50	0	1000	1150	22.4	0.2
06-001	Screening	0	0	0	0	0	13.0	20.0
06-002	Screening	0	0	0	0	0	8.1	20.0

Listing 5 - Study IP-001-09 : Uric and Lactic acid

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Uric Acid (UA)	UA unit	UA low	UA high	UA evaluation	Lactic acid (LA)	LA unit	LA low	LA high	LA evaluation
01-001	Screening	2019-10-16	3.3	mg/dl	3.5	8.5	2	.		.	.	.
	Day 0	2019-11-13	3.3	mg/dl	3.5	8.5	2	15.30	mg/dL	10.0	20	1
	Day 14	2019-11-28	7.1	mg/dl	3.5	8.5	1	14.95	mg/dL	10.0	20	1
	Day 28	2019-12-12	7.7	mg/dL	3.5	7.2	2	8.10	mg/dL	10.0	20	2
	Day 42	2019-12-23	7.2	mg/dL	3.5	7.2	1	14.40	mg/dL	10.0	20	1
	Day 56	2020-01-07	6.8	mg/dL	3.5	7.2	1	.	mg/dL	10.0	20	.
01-002	Screening	2018-11-13	4.4		.	.	1	.		.	.	.
	Day 0	2019-12-11	4.2	mg/dL	3.5	7.2	1	11.00	mg/dL	10.0	20	1
	Day 14	2019-12-27	4.7	mg/dL	3.5	7.2	1	14.00	mg/dL	10.0	20	1
	Day 28	2020-01-08	4.3	mg/dL	3.5	7.2	1	17.11	mg/dL	10.0	20	1
	Day 42	2020-01-22	4.4	mg/dL	3.5	7.2	1	10.80	mg/dL	10.0	20	1
	Day 56	2020-02-05	3.9	mg/dL	3.5	7.2	1	17.74	mg/dL	10.0	20	1
01-003	Screening	2019-11-13	5.6	mg/dl	3.5	8.5	1	.		.	.	.
	Day 0	2019-12-11	5.2	mg/dL	3.5	7.2	1	6.00	mg/dL	10.0	20	2
	Day 14	2019-12-27	5.6	mg/dL	3.5	7.2	1	5.00	mg/dL	10.0	20	2
	Day 28	2020-01-10	5.6	mg/dL	3.5	7.2	1	10.80	mg/dL	10.0	20	1
	Day 42	2020-01-22	5.2	mg/dL	3.5	7.2	1	9.00	mg/dL	10.0	20	2
	Day 56	2020-02-05	4.7	mg/dL	3.5	7.2	1	11.00	mg/dL	10.0	20	1
01-004	Screening	2019-11-15	3.7	mg/dl	2.5	6.2	1	.		.	.	.
	Day 0	2019-12-13	4.4	mg/dL	2.6	6.0	1	7.00	mg/dL	10.0	20	2
	Day 14	2019-12-27	4.7	mg/dL	2.6	6.0	1	5.00	mg/dL	10.0	20	2
	Day 28	2020-01-09	4.3	mg/dL	2.6	6.0	1	7.00	mg/dL	10.0	20	2
	Day 42	2020-01-23	4.8	mg/dL	2.6	6.0	1	5.40	mg/dL	10.0	20	2
	Day 56	2020-02-10	5.3	mg/dL	2.6	6.0	1	6.00	mg/dL	10.0	20	2
01-005	Screening	2019-11-15	5.4	mg/dl	3.5	8.5	1	.		.	.	.
	Day 0	2019-12-13	5.9	mg/dL	3.5	7.2	1	11.00	mg/dL	10.0	20	1
	Day 14	2019-12-27	5.9	mg/dL	3.5	7.2	1	8.00	mg/dL	10.0	20	2
	Day 28	2020-01-10	5.9	mg/dL	3.5	7.2	1	12.60	mg/dL	10.0	20	1
	Day 42	2020-01-24	6.1	mg/dL	3.5	7.2	1	19.80	mg/dL	10.0	20	1
	Day 56	2020-02-07	5.9	mg/dL	3.5	7.2	1	16.00	mg/dL	10.0	20	1

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 5 - Study IP-001-09 : Uric and Lactic acid

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Uric Acid (UA)	UA unit	UA low	UA high	UA evaluation	Lactic acid (LA)	LA unit	LA low	LA high	LA evaluation
01-006	Screening	2019-11-20	1.9	mg/dl	3.5	8.5	2	.		.	.	.
	Day 0	2019-12-18	9.9	mg/dL	3.5	7.2	2	9.00	mg/dL	10.0	20	2
	Day 14	2020-01-03	4.8	mg/dL	3.5	7.2	1	15.30	mg/dL	10.0	20	1
	Day 28	2020-01-15	6.9	mg/dL	3.5	7.2	1	7.20	mg/dL	10.0	20	2
	Day 42	2020-01-29	7.5	mg/dL	3.5	7.2	2	13.50	mg/dL	10.0	20	1
	Day 56	2020-02-12	7.3	mg/dL	3.5	7.2	2	8.00	mg/dL	10.0	20	2
01-007	Screening	2019-11-21	4.5	mg/dl	3.5	8.5	1	.		.	.	.
	Day 0	2019-12-19	4.3	mg/dL	3.5	7.2	1	10.00	mg/dL	10.0	20	1
	Day 14	2020-01-03	4.2	mg/dL	3.5	7.2	1	9.90	mg/dL	10.0	20	2
	Day 28	2020-01-16	4.6	mg/dL	3.5	7.2	1	11.00	mg/dL	10.0	20	1
	Day 42	2020-01-30	5.1	mg/dL	3.5	7.2	1	13.00	mg/dL	10.0	20	1
	Day 56	2020-02-13	5.2	mg/dL	3.5	7.2	1	8.00	mg/dL	10.0	20	2
01-008	Screening	2019-11-21	8.9	mg/dl	3.5	8.5	2	.		.	.	.
	Day 0	2019-12-19	.	mg/dL	3.5	7.2	.	6.00	mg/dL	10.0	20	2
	Day 14	2020-01-03	9.7	mg/dL	3.5	7.2	2	9.90	mg/dL	10.0	20	2
	Day 28	2020-01-16	7.6	mg/dL	3.5	7.2	2	9.00	mg/dL	10.0	20	2
	Day 42	2020-01-30	5.9	mg/dL	3.5	7.2	1	8.00	mg/dL	10.0	20	2
	Day 56	2020-02-13	5.9	mg/dL	3.5	7.2	1	6.00	mg/dL	10.0	20	2
01-009	Screening	2019-11-26	6.6	mg/dl	2.5	6.2	2	.		.	.	.
	Day 0	2019-12-23	6.3	mg/dL	2.6	6.0	2	7.20	mg/dL	10.0	20	2
	Day 14	2020-01-07	7.5	mg/dL	2.6	6.0	2	.	mg/dL	10.0	20	.
	Day 28	2020-01-21	6.7	mg/dL	2.6	6.0	2	10.00	mg/dL	10.0	20	1
	Day 42	2020-02-04	7.3	mg/dL	2.6	6.0	2	6.00	mg/dL	10.0	20	2
	Day 56	2020-02-18	6.2	mg/dL	2.6	6.0	2	9.90	mg/dL	10.0	20	2
01-010	Screening	2019-12-10	4.8	mg/dL	3.5	7.2	1	.		.	.	.
	Day 0	2020-01-08	4.8	mg/dL	3.5	7.2	1	8.10	mg/dL	10.0	20	2
	Day 14		.		.	.	.	.		.	.	.
	Day 28		.		.	.	.	.		.	.	.
	Day 42		.		.	.	.	.		.	.	.
	Day 56		.		.	.	.	.		.	.	.

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 5 - Study IP-001-09 : Uric and Lactic acid

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Uric Acid (UA)	UA unit	UA low	UA high	UA evaluation	Lactic acid (LA)	LA unit	LA low	LA high	LA evaluation
01-011	Screening	2020-02-06	3.3	mg/dL	2.6	6.0	1	.		.	.	.
	Day 0	2020-03-05	4.5	mg/dL	2.6	6.0	1	21.00	mg/dL	10.0	20	2
	Day 14	2020-03-20	4.3	mg/dL	2.6	6.0	1	19.80	mg/dL	10.0	20	1
	Day 28	2020-04-02	4.1	mg/dL	2.6	6.0	1	13.50	mg/dL	10.0	20	1
	Day 42	2020-04-16	5.0	mg/dL	2.6	6.0	1	.	mg/dL	10.0	20	.
	Day 56	2020-04-30	5.3	mg/dL	2.6	6.0	1	20.00	mg/dL	10.0	20	1
05-001	Screening	2021-10-13	4.0	mg/dL	3.5	7.2	1	.		.	.	.
	Day 0	2021-11-10	4.9	mg/dL	3.5	7.2	1	0.70	mmol/L	0.4	2	1
	Day 14	2021-11-26	3.7	mg/dL	3.5	7.2	1	0.90	mmol/L	0.4	2	1
	Day 28	2021-12-09	3.5	mg/dL	3.5	7.2	1	.	mmol/L	0.4	2	.
	Day 42	2021-12-28	4.5	mg/dL	3.5	7.2	1	1.10	mmol/L	0.4	2	1
	Day 56	2022-02-22	4.0	mg/dL	3.5	7.2	1	1.40	mmol/L	0.4	2	1
05-002	Screening	2021-10-29	5.0	mg/dL	3.5	7.2	1	.		.	.	.
	Day 0	2021-11-30	4.4	mg/dL	3.5	7.2	1	0.80	mmol/L	0.4	2	1
	Day 14	2021-12-14	2.7	mg/dL	3.5	7.2	2	1.10	mmol/L	0.4	2	1
	Day 28	2021-12-30	5.1	mg/dL	3.5	7.2	1	0.60	mmol/L	0.4	2	1
	Day 42	2022-01-15	4.9	mg/dL	3.5	7.2	1	0.60	mmol/L	0.4	2	1
	Day 56	2022-02-03	5.1	mg/dL	3.5	7.2	1	0.80	mmol/L	0.4	2	1
06-001	Screening	2021-12-15	3.4	mg/dL	3.5	7.0	2	.		.	.	.
06-002	Screening	2021-12-15	6.4	mg/dL	3.5	7.0	1	.		.	.	.

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 6.1 - Study IP-001-09 : Haematology - RBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	3.90	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	3.77	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	3.84	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	3.43	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	3.59	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	3.48	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-002	Screening	2018-11-13	Yes	4.15	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	4.17	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	4.06	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	4.28	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	4.09	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	4.17	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	3.34	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	3.03	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	3.03	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	2.92	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	3.20	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	3.44	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	3.42	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	3.46	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	3.51	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	3.51	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	3.41	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	3.36	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	3.27	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	3.07	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	3.22	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	3.73	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	3.91	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	3.89	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	3.80	10^6/mmc	4.50	5.30	.	Not Clinically Significant

Listing 6.1 - Study IP-001-09 : Haematology - RBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	3.92	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 14	2020-01-03	Yes	4.13	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 28	2020-01-15	Yes	4.15	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 42	2020-01-29	Yes	4.22	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 56	2020-02-12	Yes	4.26	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
01-007	Screening	2019-11-21	Yes	4.38	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 0	2019-12-19	Yes	4.21	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 14	2020-01-03	Yes	3.72	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 28	2020-01-16	Yes	3.62	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 42	2020-01-30	Yes	3.35	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 56	2020-02-13	Yes	2.95	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
01-008	Screening	2019-11-21	Yes	4.05	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 0	2019-12-19	Yes	3.91	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 14	2020-01-03	Yes	4.03	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 28	2020-01-16	Yes	3.75	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 42	2020-01-30	Yes	3.71	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 56	2020-02-13	Yes	3.53	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
01-009	Screening	2019-11-26	Yes	3.44	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 0	2019-12-23	Yes	3.50	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 14	2020-01-07	Yes	3.70	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 28	2020-01-21	Yes	3.66	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 42	2020-02-04	Yes	3.88	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 56	2020-02-18	Yes	3.84	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
01-010	Screening	2019-12-10	Yes	3.40	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 0	2020-01-08	Yes	3.71	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	4.26	10^6/mmc	4.50	5.30	.	Not Clinically Significant	
	Day 0	2020-03-05	Yes	4.48	10^6/mmc	4.50	5.30	.	Not Clinically Significant	

Listing 6.1 - Study IP-001-09 : Haematology - RBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	4.12	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	3.97	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	3.65	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	3.68	10^6/mmc	4.50	5.30	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	4.30	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	4.07	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	3.93	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	3.30	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 42	2021-12-28	Yes	3.44	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	3.89	10^6/uL	4.54	5.78	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	3.84	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	4.31	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	4.64	10^6/uL	4.54	5.78	.	Normal
	Day 28	2021-12-30	Yes	4.18	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	4.41	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	4.06	10^6/uL	4.54	5.78	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	3.31	10^12/L	4.50	5.50	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	3.67	10^12/L	4.50	5.50	.	Not Clinically Significant

Listing 6.2 - Study IP-001-09 : Haematology - Hematocrit

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	36.0	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	35.8	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	36.0	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	31.8	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	33.7	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	32.6	%	37.0	49.0	.	Not Clinically Significant
01-002	Screening	2018-11-13	Yes	38.0	%	37.0	49.0	.	Normal
	Day 0	2019-12-11	Yes	38.1	%	37.0	49.0	.	Normal
	Day 14	2019-12-27	Yes	36.8	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	39.5	%	37.0	49.0	.	Normal
	Day 42	2020-01-22	Yes	37.9	%	37.0	49.0	.	Normal
	Day 56	2020-02-05	Yes	38.8	%	37.0	49.0	.	Normal
01-003	Screening	2019-11-13	Yes	29.2	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	26.9	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	26.5	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	25.8	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	28.7	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	31.4	%	37.0	49.0	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	33.1	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	33.8	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	34.0	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	33.5	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	33.0	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	32.5	%	37.0	49.0	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	29.5	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	27.6	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	29.6	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	33.5	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	35.3	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	34.4	%	37.0	49.0	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	34.6	%	37.0	49.0	.	Not Clinically Significant

Listing 6.2 - Study IP-001-09 : Haematology - Hematocrit

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	35.1	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	37.0	%	37.0	49.0	.	Normal
	Day 28	2020-01-15	Yes	36.9	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	38.1	%	37.0	49.0	.	Normal
	Day 56	2020-02-12	Yes	37.6	%	37.0	49.0	.	Normal
01-007	Screening	2019-11-21	Yes	37.1	%	37.0	49.0	.	Normal
	Day 0	2019-12-19	Yes	35.6	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	32.5	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	30.8	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	28.7	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	25.8	%	37.0	49.0	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	36.9	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	35.6	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	36.4	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	33.9	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	34.0	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	32.4	%	37.0	49.0	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	31.6	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-12-23	Yes	31.9	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	33.0	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	33.8	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	11.8	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	34.9	%	37.0	49.0	.	Not Clinically Significant
01-010	Screening	2019-12-10	Yes	33.0	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	36.0	%	37.0	49.0	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	40.2	%	37.0	49.0	.	Normal
	Day 0	2020-03-05	Yes	42.0	%	37.0	49.0	.	Normal

Listing 6.2 - Study IP-001-09 : Haematology - Hematocrit

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	37.4	%	37.0	49.0	.	Normal
	Day 28	2020-04-02	Yes	35.3	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	32.6	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	33.3	%	37.0	49.0	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	39.9	%	38.9	50.9	.	Normal
	Day 0	2021-11-10	Yes	35.9	%	38.9	50.9	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	36.5	%	38.9	50.9	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	29.2	%	38.9	50.9	.	Not Clinically Significant
	Day 42	2021-12-28	Yes	31.5	%	38.9	50.9	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	35.1	%	38.9	50.9	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	35.4	%	38.9	50.9	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	39.1	%	38.9	50.9	.	Normal
	Day 14	2021-12-14	Yes	40.2	%	38.9	50.9	.	Normal
	Day 28	2021-12-30	Yes	35.8	%	38.9	50.9	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	36.1	%	38.9	50.9	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	33.4	%	38.9	50.9	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	31.2	%	40.0	50.0	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	35.1	%	40.0	50.0	.	Not Clinically Significant

Listing 6.3 - Study IP-001-09 : Haematology - Hemoglobin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	11.9	g/dl	13.0	16.0	.	Clinically significant for concomitant disease
	Day 0	2019-11-13	Yes	11.3	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	11.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	10.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	10.9	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	10.6	g/dl	13.0	16.0	.	Not Clinically Significant
01-002	Screening	2018-11-13	Yes	12.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	11.8	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	11.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	12.3	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	11.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	11.9	g/dl	13.0	16.0	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	9.9	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	8.9	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	8.8	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	8.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	9.3	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	10.1	g/dl	13.0	16.0	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	10.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	10.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	10.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	10.8	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	10.4	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	10.2	g/dl	13.0	16.0	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	9.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	8.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	9.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	10.4	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	11.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	10.7	g/dl	13.0	16.0	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	11.3	g/dl	13.0	16.0	.	Not Clinically Significant

Listing 6.3 - Study IP-001-09 : Haematology - Hemoglobin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	11.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	12.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	12.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	12.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	12.3	g/dl	13.0	16.0	.	Not Clinically Significant
01-007	Screening	2019-11-21	Yes	12.4	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	11.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	10.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	10.1	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	9.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	8.2	g/dl	13.0	16.0	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	11.8	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	11.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	12.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	11.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	11.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	10.5	g/dl	13.0	16.0	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	10.3	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-23	Yes	10.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	11.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	11.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	35.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	11.4	g/dl	13.0	16.0	.	Not Clinically Significant
01-010	Screening	2019-12-10	Yes	10.1	g/dl	13.0	16.0	.	Clinically sign. for the pathology under study
	Day 0	2020-01-08	Yes	11.3	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	12.6	g/dl	13.0	16.0	.	Clinically sign. for the pathology under study
	Day 0	2020-03-05	Yes	13.2	g/dl	13.0	16.0	.	Normal

Listing 6.3 - Study IP-001-09 : Haematology - Hemoglobin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	12.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	11.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	10.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	10.9	g/dl	13.0	16.0	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	12.2	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	11.6	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	11.2	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	9.4	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 42	2021-12-28	Yes	10.4	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	11.5	gr/dl	13.3	17.2	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	11.2	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	12.2	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	12.7	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	11.9	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	11.8	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	11.2	gr/dl	13.3	17.2	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	10.6	g/dL	13.0	17.0	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	12.0	g/dL	13.0	17.0	.	Not Clinically Significant

Listing 6.4 - Study IP-001-09 : Haematology - WBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	6.88	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-11-13	Yes	8.30	10^3/uL	4.0	10.0	.	Normal
	Day 14	2019-11-28	Yes	8.01	10^3/uL	4.0	10.0	.	Normal
	Day 28	2019-12-12	Yes	7.83	10^3/uL	4.0	10.0	.	Normal
	Day 42	2019-12-23	Yes	6.52	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-01-07	Yes	7.20	10^3/uL	4.0	10.0	.	Normal
01-002	Screening	2018-11-13	Yes	32.86	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	31.21	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	35.84	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	35.75	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	33.75	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	29.90	10^3/uL	4.0	10.0	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	8.17	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-12-11	Yes	8.15	10^3/uL	4.0	10.0	.	Normal
	Day 14	2019-12-27	Yes	6.17	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-10	Yes	9.45	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-01-22	Yes	6.04	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-05	Yes	6.97	10^3/uL	4.0	10.0	.	Normal
01-004	Screening	2019-11-15	Yes	6.69	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-12-13	Yes	9.13	10^3/uL	4.0	10.0	.	Normal
	Day 14	2019-12-27	Yes	7.78	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-09	Yes	8.03	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-01-23	Yes	8.09	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-10	Yes	7.59	10^3/uL	4.0	10.0	.	Normal
01-005	Screening	2019-11-15	Yes	7.86	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-12-13	Yes	6.01	10^3/uL	4.0	10.0	.	Normal
	Day 14	2019-12-27	Yes	4.75	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-10	Yes	5.23	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-01-24	Yes	5.98	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-07	Yes	6.01	10^3/uL	4.0	10.0	.	Normal
01-006	Screening	2019-11-20	Yes	6.29	10^3/uL	4.0	10.0	.	Normal

Listing 6.4 - Study IP-001-09 : Haematology - WBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	5.87	10^3/uL	4.0	10.0	.	Normal
	Day 14	2020-01-03	Yes	5.76	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-15	Yes	6.04	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-01-29	Yes	5.01	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-12	Yes	7.00	10^3/uL	4.0	10.0	.	Normal
01-007	Screening	2019-11-21	Yes	11.37	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	14.27	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	10.12	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	10.61	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	9.11	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-13	Yes	6.45	10^3/uL	4.0	10.0	.	Normal
01-008	Screening	2019-11-21	Yes	7.63	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-12-19	Yes	6.05	10^3/uL	4.0	10.0	.	Normal
	Day 14	2020-01-03	Yes	8.24	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-16	Yes	6.49	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-01-30	Yes	6.40	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-13	Yes	7.31	10^3/uL	4.0	10.0	.	Normal
01-009	Screening	2019-11-26	Yes	4.82	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-12-23	Yes	4.68	10^3/uL	4.0	10.0	.	Normal
	Day 14	2020-01-07	Yes	4.58	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-21	Yes	4.90	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-02-04	Yes	4.27	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-18	Yes	5.18	10^3/uL	4.0	10.0	.	Normal
01-010	Screening	2019-12-10	Yes	4.59	10^3/uL	4.0	10.0	.	Normal
	Day 0	2020-01-08	Yes	4.28	10^3/uL	4.0	10.0	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	7.79	10^3/uL	4.0	10.0	.	Normal
	Day 0	2020-03-05	Yes	6.52	10^3/uL	4.0	10.0	.	Normal

Listing 6.4 - Study IP-001-09 : Haematology - WBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	8.32	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-04-02	Yes	8.29	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-04-16	Yes	8.88	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-04-30	Yes	7.99	10^3/uL	4.0	10.0	.	Normal
05-001	Screening	2021-10-13	No	5.45	10^3/uL	3.7	9.7	.	Normal
	Day 0	2021-11-10	Yes	4.19	10^3/uL	3.7	9.7	.	Normal
	Day 14	2021-11-26	Yes	5.97	10^3/uL	3.7	9.7	.	Normal
	Day 28	2021-12-09	Yes	5.27	10^3/uL	3.7	9.7	.	Normal
	Day 42	2021-12-28	Yes	4.75	10^3/uL	3.7	9.7	.	Normal
	Day 56	2022-02-22	Yes	5.81	10^3/uL	3.7	9.7	.	Normal
05-002	Screening	2021-10-29	Yes	9.53	10^3/uL	3.7	9.7	.	Normal
	Day 0	2021-11-30	Yes	11.04	10^3/uL	3.7	9.7	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	8.88	10^3/uL	3.7	9.7	.	Normal
	Day 28	2021-12-30	Yes	6.73	10^3/uL	3.7	9.7	.	Normal
	Day 42	2022-01-15	Yes	9.18	10^3/uL	3.7	9.7	.	Normal
	Day 56	2022-02-03	Yes	7.66	10^3/uL	3.7	9.7	.	Normal
06-001	Screening	2021-12-15	Yes	6.94	10^9/L	4.0	10.0	.	Normal
06-002	Screening	2021-12-15	Yes	5.83	10^9/L	4.0	10.0	.	Not Clinically Significant

Listing 6.5 - Study IP-001-09 : Haematology - Neutrophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	3.82	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-11-13	Yes	5.05	10^3/uL	2.1	7.1	.	Normal
	Day 14	2019-11-28	Yes	4.39	10^3/uL	2.1	7.1	.	Normal
	Day 28	2019-12-12	Yes	4.96	10^3/uL	2.1	7.1	.	Normal
	Day 42	2019-12-23	Yes	3.47	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-01-07	Yes	4.32	10^3/uL	2.1	7.1	.	Normal
01-002	Screening	2018-11-13	Yes	3.89	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-11	Yes	3.57	10^3/uL	2.1	7.1	.	Normal
	Day 14	2019-12-27	Yes	4.07	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-08	Yes	7.75	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	5.19	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-05	Yes	3.26	10^3/uL	2.1	7.1	.	Normal
01-003	Screening	2019-11-13	Yes	6.14	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-11	Yes	5.88	10^3/uL	2.1	7.1	.	Normal
	Day 14	2019-12-27	Yes	4.37	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-10	Yes	7.77	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	4.33	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-05	Yes	4.98	10^3/uL	2.1	7.1	.	Normal
01-004	Screening	2019-11-15	Yes	4.72	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-13	Yes	6.72	10^3/uL	2.1	7.1	.	Normal
	Day 14	2019-12-27	Yes	6.09	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-09	Yes	5.96	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-01-23	Yes	6.09	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-10	Yes	5.66	10^3/uL	2.1	7.1	.	Normal
01-005	Screening	2019-11-15	Yes	6.05	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-13	Yes	4.42	10^3/uL	2.1	7.1	.	Normal
	Day 14	2019-12-27	Yes	3.48	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-10	Yes	3.62	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-01-24	Yes	4.21	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-07	Yes	4.07	10^3/uL	2.1	7.1	.	Normal
01-006	Screening	2019-11-20	Yes	3.85	10^3/uL	2.1	7.1	.	Normal

Listing 6.5 - Study IP-001-09 : Haematology - Neutrophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	3.67	10^3/uL	2.1	7.1	.	Normal
	Day 14	2020-01-03	Yes	3.50	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-15	Yes	3.84	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-01-29	Yes	2.80	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-12	Yes	4.78	10^3/uL	2.1	7.1	.	Normal
01-007	Screening	2019-11-21	Yes	9.24	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	11.35	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	7.63	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	8.11	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	6.52	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-13	Yes	3.82	10^3/uL	2.1	7.1	.	Normal
01-008	Screening	2019-11-21	Yes	4.88	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-19	Yes	4.03	10^3/uL	2.1	7.1	.	Normal
	Day 14	2020-01-03	Yes	4.84	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-16	Yes	4.11	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-01-30	Yes	3.81	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-13	Yes	4.68	10^3/uL	2.1	7.1	.	Normal
01-009	Screening	2019-11-26	Yes	2.56	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-23	Yes	2.52	10^3/uL	2.1	7.1	.	Normal
	Day 14	2020-01-07	Yes	2.72	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-21	Yes	2.93	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-02-04	Yes	2.50	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-18	Yes	3.02	10^3/uL	2.1	7.1	.	Normal
01-010	Screening	2019-12-10	Yes	3.19	10^3/uL	2.1	7.1	.	Normal
	Day 0	2020-01-08	Yes	3.02	10^3/uL	2.1	7.1	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	5.10	10^3/uL	2.1	7.1	.	Normal
	Day 0	2020-03-05	Yes	4.45	10^3/uL	2.1	7.1	.	Normal

Listing 6.5 - Study IP-001-09 : Haematology - Neutrophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	5.86	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-04-02	Yes	6.19	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-04-16	Yes	5.98	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-04-30	Yes	5.54	10^3/uL	2.1	7.1	.	Normal
05-001	Screening	2021-10-13	No	58.90	%	42.9	78.4	.	Normal
	Day 0	2021-11-10	Yes	50.00	%	42.9	78.4	.	Normal
	Day 14	2021-11-26	Yes	62.20	%	42.9	78.4	.	Normal
	Day 28	2021-12-09	Yes	61.20	%	42.9	78.4	.	Normal
	Day 42	2021-12-28	Yes	55.20	%	42.9	78.4	.	Normal
	Day 56	2022-02-22	Yes	67.30	%	42.9	78.4	.	Normal
05-002	Screening	2021-10-29	Yes	81.70	%	42.9	78.4	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	78.50	%	42.9	78.4	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	70.80	%	42.9	78.4	.	Normal
	Day 28	2021-12-30	Yes	73.70	%	42.9	78.4	.	Normal
	Day 42	2022-01-15	Yes	74.40	%	42.9	78.4	.	Normal
	Day 56	2022-02-03	Yes	70.70	%	42.9	78.4	.	Normal
06-001	Screening	2021-12-15	Yes	70.90	%	40.0	80.0	.	Normal
06-002	Screening	2021-12-15	Yes	64.00	%	40.0	80.0	.	Not Clinically Significant

Listing 6.6 - Study IP-001-09 : Haematology - Basophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	0.01	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-11-13	Yes	0.01	10^3/uL	0.0	0.2	.	Normal
	Day 14	2019-11-28	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 28	2019-12-12	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 42	2019-12-23	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-01-07	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
01-002	Screening	2018-11-13	Yes	0.11	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-12-11	Yes	0.09	10^3/uL	0.0	0.2	.	Normal
	Day 14	2019-12-27	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-08	Yes	0.09	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-01-22	Yes	0.11	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-05	Yes	0.09	10^3/uL	0.0	0.2	.	Normal
01-003	Screening	2019-11-13	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-12-11	Yes	0.04	10^3/uL	0.0	0.2	.	Normal
	Day 14	2019-12-27	Yes	0.01	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-10	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-01-22	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-05	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
01-004	Screening	2019-11-15	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-12-13	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 14	2019-12-27	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-09	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-01-23	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-10	Yes	0.04	10^3/uL	0.0	0.2	.	Normal
01-005	Screening	2019-11-15	Yes	0.08	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-12-13	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 14	2019-12-27	Yes	0.03	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-10	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-01-24	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-07	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
01-006	Screening	2019-11-20	Yes	0.06	10^3/uL	0.0	0.2	.	Normal

Listing 6.6 - Study IP-001-09 : Haematology - Basophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	0.04	10^3/uL	0.0	0.2	.	Normal
	Day 14	2020-01-03	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-15	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-01-29	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-12	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
01-007	Screening	2019-11-21	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-12-19	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 14	2020-01-03	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-16	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-01-30	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-13	Yes	0.03	10^3/uL	0.0	0.2	.	Normal
01-008	Screening	2019-11-21	Yes	0.09	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-12-19	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 14	2020-01-03	Yes	0.10	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-16	Yes	0.10	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-01-30	Yes	0.09	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-13	Yes	0.08	10^3/uL	0.0	0.2	.	Normal
01-009	Screening	2019-11-26	Yes	0.05	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-12-23	Yes	0.04	10^3/uL	0.0	0.2	.	Normal
	Day 14	2020-01-07	Yes	0.05	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-21	Yes	0.03	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-02-04	Yes	0.04	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-18	Yes	0.04	10^3/uL	0.0	0.2	.	Normal
01-010	Screening	2019-12-10	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 0	2020-01-08	Yes	0.01	10^3/uL	0.0	0.2	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	0.04	10^3/uL	0.0	0.2	.	Normal
	Day 0	2020-03-05	Yes	0.04	10^3/uL	0.0	0.2	.	Normal

Listing 6.6 - Study IP-001-09 : Haematology - Basophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	0.03	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-04-02	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-04-16	Yes	0.05	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-04-30	Yes	0.05	10^3/uL	0.0	0.2	.	Normal
05-001	Screening	2021-10-13	No	0.40	%	0.3	1.3	.	Normal
	Day 0	2021-11-10	Yes	0.50	%	0.3	1.3	.	Normal
	Day 14	2021-11-26	Yes	0.50	%	0.3	1.3	.	Normal
	Day 28	2021-12-09	Yes	0.30	%	0.3	1.3	.	Normal
	Day 42	2021-12-28	Yes	1.20	%	0.3	1.3	.	Normal
	Day 56	2022-02-22	Yes	0.50	%	0.3	1.3	.	Normal
05-002	Screening	2021-10-29	Yes	0.50	%	0.3	1.3	.	Normal
	Day 0	2021-11-30	Yes	0.40	%	0.3	1.3	.	Normal
	Day 14	2021-12-14	Yes	0.70	%	0.3	1.3	.	Normal
	Day 28	2021-12-30	Yes	0.90	%	0.3	1.3	.	Normal
	Day 42	2022-01-15	Yes	1.20	%	0.3	1.3	.	Normal
	Day 56	2022-02-03	Yes	0.60	%	0.3	1.3	.	Normal
06-001	Screening	2021-12-15	Yes	0.20	%	0.0	1.2	.	Normal
06-002	Screening	2021-12-15	Yes	0.40	%	0.0	1.2	.	Not Clinically Significant

Listing 6.7 - Study IP-001-09 : Haematology - Eosinophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done		Evaluation
01-001	Screening	2019-10-16	Yes	0.14	10^3/uL	0.0	0.5	.	Normal	
	Day 0	2019-11-13	Yes	0.19	10^3/uL	0.0	0.5	.	Normal	
	Day 14	2019-11-28	Yes	0.21	10^3/uL	0.0	0.5	.	Normal	
	Day 28	2019-12-12	Yes	0.22	10^3/uL	0.0	0.5	.	Normal	
	Day 42	2019-12-23	Yes	0.13	10^3/uL	0.0	0.5	.	Normal	
	Day 56	2020-01-07	Yes	0.20	10^3/uL	0.0	0.5	.	Normal	
01-002	Screening	2018-11-13	Yes	0.30	10^3/uL	0.0	0.5	.	Normal	
	Day 0	2019-12-11	Yes	0.31	10^3/uL	0.0	0.5	.	Normal	
	Day 14	2019-12-27	Yes	0.24	10^3/uL	0.0	0.5	.	Normal	
	Day 28	2020-01-08	Yes	0.23	10^3/uL	0.0	0.5	.	Normal	
	Day 42	2020-01-22	Yes	0.23	10^3/uL	0.0	0.5	.	Normal	
	Day 56	2020-02-05	Yes	0.24	10^3/uL	0.0	0.5	.	Normal	
01-003	Screening	2019-11-13	Yes	0.00	10^3/uL	0.0	0.5	.	Normal	
	Day 0	2019-12-11	Yes	0.00	10^3/uL	0.0	0.5	.	Normal	
	Day 14	2019-12-27	Yes	0.00	10^3/uL	0.0	0.5	.	Normal	
	Day 28	2020-01-10	Yes	0.00	10^3/uL	0.0	0.5	.	Normal	
	Day 42	2020-01-22	Yes	0.00	10^3/uL	0.0	0.5	.	Normal	
	Day 56	2020-02-05	Yes	0.00	10^3/uL	0.0	0.5	.	Normal	
01-004	Screening	2019-11-15	Yes	0.27	10^3/uL	0.0	0.5	.	Normal	
	Day 0	2019-12-13	Yes	0.35	10^3/uL	0.0	0.5	.	Normal	
	Day 14	2019-12-27	Yes	0.20	10^3/uL	0.0	0.5	.	Normal	
	Day 28	2020-01-09	Yes	0.29	10^3/uL	0.0	0.5	.	Normal	
	Day 42	2020-01-23	Yes	0.26	10^3/uL	0.0	0.5	.	Normal	
	Day 56	2020-02-10	Yes	0.26	10^3/uL	0.0	0.5	.	Normal	
01-005	Screening	2019-11-15	Yes	0.13	10^3/uL	0.0	0.5	.	Normal	
	Day 0	2019-12-13	Yes	0.14	10^3/uL	0.0	0.5	.	Normal	
	Day 14	2019-12-27	Yes	0.10	10^3/uL	0.0	0.5	.	Normal	
	Day 28	2020-01-10	Yes	0.09	10^3/uL	0.0	0.5	.	Normal	
	Day 42	2020-01-24	Yes	0.08	10^3/uL	0.0	0.5	.	Normal	
	Day 56	2020-02-07	Yes	0.12	10^3/uL	0.0	0.5	.	Normal	
01-006	Screening	2019-11-20	Yes	0.26	10^3/uL	0.0	0.5	.	Normal	

Listing 6.7 - Study IP-001-09 : Haematology - Eosinophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	0.24	10^3/uL	0.0	0.5	.	Normal
	Day 14	2020-01-03	Yes	0.25	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-15	Yes	0.27	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-01-29	Yes	0.37	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-12	Yes	0.27	10^3/uL	0.0	0.5	.	Normal
01-007	Screening	2019-11-21	Yes	0.31	10^3/uL	0.0	0.5	.	Normal
	Day 0	2019-12-19	Yes	0.65	10^3/uL	0.0	0.5	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	0.43	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-16	Yes	0.48	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-01-30	Yes	0.45	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-13	Yes	0.26	10^3/uL	0.0	0.5	.	Normal
01-008	Screening	2019-11-21	Yes	0.46	10^3/uL	0.0	0.5	.	Normal
	Day 0	2019-12-19	Yes	0.18	10^3/uL	0.0	0.5	.	Normal
	Day 14	2020-01-03	Yes	0.34	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-16	Yes	0.30	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-01-30	Yes	0.26	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-13	Yes	0.25	10^3/uL	0.0	0.5	.	Normal
01-009	Screening	2019-11-26	Yes	0.24	10^3/uL	0.0	0.5	.	Normal
	Day 0	2019-12-23	Yes	0.17	10^3/uL	0.0	0.5	.	Normal
	Day 14	2020-01-07	Yes	0.12	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-21	Yes	0.17	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-02-04	Yes	0.13	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-18	Yes	0.19	10^3/uL	0.0	0.5	.	Normal
01-010	Screening	2019-12-10	Yes	0.25	10^3/uL	0.0	0.5	.	Normal
	Day 0	2020-01-08	Yes	0.26	10^3/uL	0.0	0.5	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	0.53	10^3/uL	0.0	0.5	.	Not Clinically Significant
	Day 0	2020-03-05	Yes	0.51	10^3/uL	0.0	0.5	.	Not Clinically Significant

Listing 6.7 - Study IP-001-09 : Haematology - Eosinophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	0.37	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-04-02	Yes	0.22	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-04-16	Yes	0.66	10^3/uL	0.0	0.5	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	0.58	10^3/uL	0.0	0.5	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	2.30	%	0.3	6.2	.	Normal
	Day 0	2021-11-10	Yes	1.30	%	0.3	6.2	.	Normal
	Day 14	2021-11-26	Yes	2.40	%	0.3	6.2	.	Normal
	Day 28	2021-12-09	Yes	1.80	%	0.3	6.2	.	Normal
	Day 42	2021-12-28	Yes	3.20	%	0.3	6.2	.	Normal
	Day 56	2022-02-22	Yes	2.50	%	0.3	6.2	.	Normal
05-002	Screening	2021-10-29	Yes	1.10	%	0.3	6.2	.	Normal
	Day 0	2021-11-30	Yes	1.60	%	0.3	6.2	.	Normal
	Day 14	2021-12-14	Yes	2.20	%	0.3	6.2	.	Normal
	Day 28	2021-12-30	Yes	2.70	%	0.3	6.2	.	Normal
	Day 42	2022-01-15	Yes	1.30	%	0.3	6.2	.	Normal
	Day 56	2022-02-03	Yes	2.00	%	0.3	6.2	.	Normal
06-001	Screening	2021-12-15	Yes	2.70	%	0.0	5.4	.	Normal
06-002	Screening	2021-12-15	Yes	3.70	%	0.0	5.4	.	Not Clinically Significant

Listing 6.8 - Study IP-001-09 : Haematology - Lymphocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	2.24	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-11-13	Yes	2.28	10^3/uL	1.1	3.0	.	Normal
	Day 14	2019-11-28	Yes	2.54	10^3/uL	1.1	3.0	.	Normal
	Day 28	2019-12-12	Yes	1.82	10^3/uL	1.1	3.0	.	Normal
	Day 42	2019-12-23	Yes	2.08	10^3/uL	1.1	3.0	.	Normal
	Day 56	2020-01-07	Yes	1.81	10^3/uL	1.1	3.0	.	Normal
01-002	Screening	2018-11-13	Yes	28.04	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	26.73	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	30.19	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	26.84	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	27.81	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	25.78	10^3/uL	1.1	3.0	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	1.66	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-12-11	Yes	1.75	10^3/uL	1.1	3.0	.	Normal
	Day 14	2019-12-27	Yes	1.36	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-01-10	Yes	1.15	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-01-22	Yes	1.37	10^3/uL	1.1	3.0	.	Normal
	Day 56	2020-02-05	Yes	1.64	10^3/uL	1.1	3.0	.	Normal
01-004	Screening	2019-11-15	Yes	1.21	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-12-13	Yes	1.18	10^3/uL	1.1	3.0	.	Normal
	Day 14	2019-12-27	Yes	0.99	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	1.17	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-01-23	Yes	1.08	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	1.07	10^3/uL	1.1	3.0	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	0.99	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	0.83	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	0.68	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	0.96	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	1.03	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	1.15	10^3/uL	1.1	3.0	.	Normal
01-006	Screening	2019-11-20	Yes	1.36	10^3/uL	1.1	3.0	.	Normal

Listing 6.8 - Study IP-001-09 : Haematology - Lymphocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	1.29	10^3/uL	1.1	3.0	.	Normal
	Day 14	2020-01-03	Yes	1.34	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-01-15	Yes	1.25	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-01-29	Yes	1.01	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	1.19	10^3/uL	1.1	3.0	.	Normal
01-007	Screening	2019-11-21	Yes	1.15	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-12-19	Yes	1.19	10^3/uL	1.1	3.0	.	Normal
	Day 14	2020-01-03	Yes	1.14	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-01-16	Yes	1.11	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-01-30	Yes	1.18	10^3/uL	1.1	3.0	.	Normal
	Day 56	2020-02-13	Yes	1.44	10^3/uL	1.1	3.0	.	Normal
01-008	Screening	2019-11-21	Yes	1.54	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-12-19	Yes	1.28	10^3/uL	1.1	3.0	.	Normal
	Day 14	2020-01-03	Yes	2.18	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-01-16	Yes	1.34	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-01-30	Yes	1.60	10^3/uL	1.1	3.0	.	Normal
	Day 56	2020-02-13	Yes	1.66	10^3/uL	1.1	3.0	.	Normal
01-009	Screening	2019-11-26	Yes	1.43	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-12-23	Yes	1.38	10^3/uL	1.1	3.0	.	Normal
	Day 14	2020-01-07	Yes	1.15	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-01-21	Yes	1.23	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-02-04	Yes	1.07	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	1.32	10^3/uL	1.1	3.0	.	Normal
01-010	Screening	2019-12-10	Yes	0.80	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	0.69	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	1.40	10^3/uL	1.1	3.0	.	Normal
	Day 0	2020-03-05	Yes	1.06	10^3/uL	1.1	3.0	.	Not Clinically Significant

Listing 6.8 - Study IP-001-09 : Haematology - Lymphocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	1.40	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-04-02	Yes	1.20	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-04-16	Yes	1.44	10^3/uL	1.1	3.0	.	Normal
	Day 56	2020-04-30	Yes	1.14	10^3/uL	1.1	3.0	.	Normal
05-001	Screening	2021-10-13	No	26.90	%	14.1	45.8	.	Normal
	Day 0	2021-11-10	Yes	29.60	%	14.1	45.8	.	Normal
	Day 14	2021-11-26	Yes	24.80	%	14.1	45.8	.	Normal
	Day 28	2021-12-09	Yes	27.30	%	14.1	45.8	.	Normal
	Day 42	2021-12-28	Yes	30.20	%	14.1	45.8	.	Normal
	Day 56	2022-02-22	Yes	20.40	%	14.1	45.8	.	Normal
05-002	Screening	2021-10-29	Yes	9.00	%	14.1	45.8	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	11.50	%	14.1	45.8	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	18.70	%	14.1	45.8	.	Normal
	Day 28	2021-12-30	Yes	15.20	%	14.1	45.8	.	Normal
	Day 42	2022-01-15	Yes	13.90	%	14.1	45.8	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	17.60	%	14.1	45.8	.	Normal
06-001	Screening	2021-12-15	Yes	17.20	%	20.0	40.0	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	27.10	%	20.0	40.0	.	Not Clinically Significant

Listing 6.9 - Study IP-001-09 : Haematology - Monocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	0.67	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-11-13	Yes	0.77	10^3/uL	0.2	0.96	.	Normal
	Day 14	2019-11-28	Yes	0.85	10^3/uL	0.2	0.96	.	Normal
	Day 28	2019-12-12	Yes	0.81	10^3/uL	0.2	0.96	.	Normal
	Day 42	2019-12-23	Yes	0.82	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-01-07	Yes	0.85	10^3/uL	0.2	0.96	.	Normal
01-002	Screening	2018-11-13	Yes	0.52	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-11	Yes	0.51	10^3/uL	0.2	0.96	.	Normal
	Day 14	2019-12-27	Yes	1.28	10^3/uL	0.2	0.96	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	0.84	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-22	Yes	0.41	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-05	Yes	0.53	10^3/uL	0.2	0.96	.	Normal
01-003	Screening	2019-11-13	Yes	0.35	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-11	Yes	0.48	10^3/uL	0.2	0.96	.	Normal
	Day 14	2019-12-27	Yes	0.43	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-10	Yes	0.51	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-22	Yes	0.32	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-05	Yes	0.33	10^3/uL	0.2	0.96	.	Normal
01-004	Screening	2019-11-15	Yes	0.43	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-13	Yes	0.81	10^3/uL	0.2	0.96	.	Normal
	Day 14	2019-12-27	Yes	0.43	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-09	Yes	0.54	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-23	Yes	0.59	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-10	Yes	0.56	10^3/uL	0.2	0.96	.	Normal
01-005	Screening	2019-11-15	Yes	0.61	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-13	Yes	0.56	10^3/uL	0.2	0.96	.	Normal
	Day 14	2019-12-27	Yes	0.46	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-10	Yes	0.49	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-24	Yes	0.59	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-07	Yes	0.61	10^3/uL	0.2	0.96	.	Normal
01-006	Screening	2019-11-20	Yes	0.76	10^3/uL	0.2	0.96	.	Normal

Listing 6.9 - Study IP-001-09 : Haematology - Monocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	0.63	10^3/uL	0.2	0.96	.	Normal
	Day 14	2020-01-03	Yes	0.61	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-15	Yes	0.62	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-29	Yes	0.77	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-12	Yes	0.69	10^3/uL	0.2	0.96	.	Normal
01-007	Screening	2019-11-21	Yes	0.61	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-19	Yes	1.02	10^3/uL	0.2	0.96	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	0.86	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-16	Yes	0.85	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-30	Yes	0.90	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-13	Yes	0.90	10^3/uL	0.2	0.96	.	Normal
01-008	Screening	2019-11-21	Yes	0.66	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-19	Yes	0.49	10^3/uL	0.2	0.96	.	Normal
	Day 14	2020-01-03	Yes	0.78	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-16	Yes	0.64	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-30	Yes	0.64	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-13	Yes	0.64	10^3/uL	0.2	0.96	.	Normal
01-009	Screening	2019-11-26	Yes	0.54	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-23	Yes	0.57	10^3/uL	0.2	0.96	.	Normal
	Day 14	2020-01-07	Yes	0.54	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-21	Yes	0.54	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-02-04	Yes	0.53	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-18	Yes	0.61	10^3/uL	0.2	0.96	.	Normal
01-010	Screening	2019-12-10	Yes	0.33	10^3/uL	0.2	0.96	.	Normal
	Day 0	2020-01-08	Yes	0.30	10^3/uL	0.2	0.96	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	0.72	10^3/uL	0.2	0.96	.	Normal
	Day 0	2020-03-05	Yes	0.46	10^3/uL	0.2	0.96	.	Normal

Listing 6.9 - Study IP-001-09 : Haematology - Monocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	0.66	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-04-02	Yes	0.66	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-04-16	Yes	0.75	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-04-30	Yes	0.68	10^3/uL	0.2	0.96	.	Normal
05-001	Screening	2021-10-13	No	11.60	%	3.3	9.20	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	18.50	%	3.3	9.20	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	10.10	%	3.3	9.20	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	9.30	%	3.3	9.20	.	Not Clinically Significant
	Day 42	2021-12-28	Yes	10.10	%	3.3	9.20	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	9.30	%	3.3	9.20	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	7.60	%	3.3	9.20	.	Normal
	Day 0	2021-11-30	Yes	8.00	%	3.3	9.20	.	Normal
	Day 14	2021-12-14	Yes	7.50	%	3.3	9.20	.	Normal
	Day 28	2021-12-30	Yes	7.50	%	3.3	9.20	.	Normal
	Day 42	2022-01-15	Yes	9.20	%	3.3	9.20	.	Normal
	Day 56	2022-02-03	Yes	9.00	%	3.3	9.20	.	Normal
06-001	Screening	2021-12-15	Yes	9.10	%	2.0	10.00	.	Normal
06-002	Screening	2021-12-15	Yes	2.80	%	2.0	10.00	.	Normal

Listing 6.10 - Study IP-001-09 : Haematology - Platelets count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	153	10^3/mmc	150	450	.	Normal
	Day 0	2019-11-13	Yes	159	10^3/mmc	150	450	.	Normal
	Day 14	2019-11-28	Yes	170	10^3/mmc	150	450	.	Normal
	Day 28	2019-12-12	Yes	178	10^3/mmc	150	450	.	Normal
	Day 42	2019-12-23	Yes	172	10^3/mmc	150	450	.	Normal
	Day 56	2020-01-07	Yes	152	10^3/mmc	150	450	.	Normal
01-002	Screening	2018-11-13	Yes	139	10^3/mmc	150	450	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	132	10^3/mmc	150	450	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	122	10^3/mmc	150	450	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	134	10^3/mmc	150	450	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	173	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-05	Yes	133	10^3/mmc	150	450	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	180	10^3/mmc	150	450	.	Normal
	Day 0	2019-12-11	Yes	208	10^3/mmc	150	450	.	Normal
	Day 14	2019-12-27	Yes	161	10^3/mmc	150	450	.	Normal
	Day 28	2020-01-10	Yes	221	10^3/mmc	150	450	.	Normal
	Day 42	2020-01-22	Yes	231	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-05	Yes	191	10^3/mmc	150	450	.	Normal
01-004	Screening	2019-11-15	Yes	299	10^3/mmc	150	450	.	Normal
	Day 0	2019-12-13	Yes	301	10^3/mmc	150	450	.	Normal
	Day 14	2019-12-27	Yes	342	10^3/mmc	150	450	.	Normal
	Day 28	2020-01-09	Yes	344	10^3/mmc	150	450	.	Normal
	Day 42	2020-01-23	Yes	243	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-10	Yes	314	10^3/mmc	150	450	.	Normal
01-005	Screening	2019-11-15	Yes	228	10^3/mmc	150	450	.	Normal
	Day 0	2019-12-13	Yes	226	10^3/mmc	150	450	.	Normal
	Day 14	2019-12-27	Yes	224	10^3/mmc	150	450	.	Normal
	Day 28	2020-01-10	Yes	288	10^3/mmc	150	450	.	Normal
	Day 42	2020-01-24	Yes	257	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-07	Yes	252	10^3/mmc	150	450	.	Normal
01-006	Screening	2019-11-20	Yes	225	10^3/mmc	150	450	.	Normal

Listing 6.10 - Study IP-001-09 : Haematology - Platelets count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	225	10^3/mmc	150	450	.	Normal	
	Day 14	2020-01-03	Yes	226	10^3/mmc	150	450	.	Normal	
	Day 28	2020-01-15	Yes	247	10^3/mmc	150	450	.	Normal	
	Day 42	2020-01-29	Yes	204	10^3/mmc	150	450	.	Normal	
	Day 56	2020-02-12	Yes	214	10^3/mmc	150	450	.	Normal	
01-007	Screening	2019-11-21	Yes	236	10^3/mmc	150	450	.	Normal	
	Day 0	2019-12-19	Yes	299	10^3/mmc	150	450	.	Normal	
	Day 14	2020-01-03	Yes	288	10^3/mmc	150	450	.	Normal	
	Day 28	2020-01-16	Yes	231	10^3/mmc	150	450	.	Normal	
	Day 42	2020-01-30	Yes	289	10^3/mmc	150	450	.	Normal	
	Day 56	2020-02-13	Yes	312	10^3/mmc	150	450	.	Normal	
01-008	Screening	2019-11-21	Yes	256	10^3/mmc	150	450	.	Normal	
	Day 0	2019-12-19	Yes	263	10^3/mmc	150	450	.	Normal	
	Day 14	2020-01-03	Yes	333	10^3/mmc	150	450	.	Normal	
	Day 28	2020-01-16	Yes	305	10^3/mmc	150	450	.	Normal	
	Day 42	2020-01-30	Yes	260	10^3/mmc	150	450	.	Normal	
	Day 56	2020-02-13	Yes	399	10^3/mmc	150	450	.	Normal	
01-009	Screening	2019-11-26	Yes	234	10^3/mmc	150	450	.	Normal	
	Day 0	2019-12-23	Yes	216	10^3/mmc	150	450	.	Normal	
	Day 14	2020-01-07	Yes	214	10^3/mmc	150	450	.	Normal	
	Day 28	2020-01-21	Yes	234	10^3/mmc	150	450	.	Normal	
	Day 42	2020-02-04	Yes	218	10^3/mmc	150	450	.	Normal	
	Day 56	2020-02-18	Yes	233	10^3/mmc	150	450	.	Normal	
01-010	Screening	2019-12-10	Yes	116	10^3/mmc	150	450	.	Not Clinically Significant	
	Day 0	2020-01-08	Yes	117	10^3/mmc	150	450	.	Not Clinically Significant	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	209	10^3/mmc	150	450	.	Normal	
	Day 0	2020-03-05	Yes	187	10^3/mmc	150	450	.	Normal	

Listing 6.10 - Study IP-001-09 : Haematology - Platelets count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	205	10^3/mmc	150	450	.	Normal
	Day 28	2020-04-02	Yes	226	10^3/mmc	150	450	.	Normal
	Day 42	2020-04-16	Yes	215	10^3/mmc	150	450	.	Normal
	Day 56	2020-04-30	Yes	226	10^3/mmc	150	450	.	Normal
05-001	Screening	2021-10-13	No	229	10^3/uL	179	373	.	Normal
	Day 0	2021-11-10	Yes	242	10^3/uL	179	373	.	Normal
	Day 14	2021-11-26	Yes	315	10^3/uL	179	373	.	Normal
	Day 28	2021-12-09	Yes	293	10^3/uL	179	373	.	Normal
	Day 42	2021-12-28	Yes	301	10^3/uL	179	373	.	Normal
	Day 56	2022-02-22	Yes	317	10^3/uL	179	373	.	Normal
05-002	Screening	2021-10-29	Yes	367	10^3/uL	179	373	.	Normal
	Day 0	2021-11-30	Yes	349	10^3/uL	179	373	.	Normal
	Day 14	2021-12-14	Yes	328	10^3/uL	179	373	.	Normal
	Day 28	2021-12-30	Yes	243	10^3/uL	179	373	.	Normal
	Day 42	2022-01-15	Yes	287	10^3/uL	179	373	.	Normal
	Day 56	2022-02-03	Yes	330	10^3/uL	179	373	.	Normal
06-001	Screening	2021-12-15	Yes	162	10^9/L	150	450	.	Normal
06-002	Screening	2021-12-15	Yes	207	10^9/L	150	450	.	Not Clinically Significant

Listing 7.1 - Study IP-001-09 : Biochemistry - BUN

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	75.80	mg/dL	9	20.0	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	79.70	mg/dL	9	20.0	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	82.10	mg/dL	9	20.0	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	81.20	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	81.20	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	81.20	mg/dL	18	55.0	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	75.50	mg/dL	9	20.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	169.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	112.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	83.54	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	84.94	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	72.80	mg/dL	18	55.0	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	99.80	mg/dL	9	20.0	.	Clinically significant for concomitant disease
	Day 0	2019-12-11	Yes	219.00	mg/dL	19	44.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	215.00	mg/dL	19	44.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	186.00	mg/dL	19	44.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	178.00	mg/dL	19	44.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	154.00	mg/dL	19	44.0	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	83.70	mg/dL	7	17.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	163.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	201.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	190.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	195.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	192.00	mg/dL	21	42.8	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	52.00	mg/dL	9	20.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	164.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	119.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	113.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	122.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	127.00	mg/dL	18	55.0	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	65.20	mg/dL	9	20.0	.	Not Clinically Significant

Listing 7.1 - Study IP-001-09 : Biochemistry - BUN

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	113.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	133.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	112.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	103.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	132.00	mg/dL	18	55.0	.	Not Clinically Significant
01-007	Screening	2019-11-21	No	83.80	mg/dL	9	20.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	202.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	225.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	245.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	209.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	188.00	mg/dL	18	55.0	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	106.40	mg/dL	9	20.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	201.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	96.60	mg/dL	18	55.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	98.94	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	86.80	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	80.27	mg/dL	18	55.0	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	77.00	mg/dL	7	17.0	.	Clinically sign. for the pathology under study
	Day 0	2019-12-23	Yes	179.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	207.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	168.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	181.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	169.00	mg/dL	21	42.8	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	91.12	mg/dL	18	55.0	.	Clinically sign. for the pathology under study
	Day 0	2020-01-08	Yes	230.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	81.77	mg/dL	21	42.8	.	Clinically sign. for the pathology under study
	Day 0	2020-03-05	Yes	74.20	mg/dL	21	42.8	.	Not Clinically Significant

Listing 7.1 - Study IP-001-09 : Biochemistry - BUN

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	159.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	87.74	mg/dL	21	42.8	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	98.47	mg/dL	21	42.8	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	86.80	mg/dL	21	42.8	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	194.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	177.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	260.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	246.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	228.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	232.00	mg/dL	15	38.0	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	163.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	165.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	149.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	182.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	157.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	156.00	mg/dL	15	38.0	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	75.00	mg/dL	10	23.0	.	Clinically significant for concomitant disease
06-002	Screening	2021-12-15	Yes	64.00	mg/dL	10	23.0	.	Clinically significant for concomitant disease

Listing 7.2 - Study IP-001-09 : Biochemistry - Creatinine

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	9.15	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	8.25	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	9.21	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	8.82	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	8.59	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	8.95	mg/dL	0.72	1.25	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	7.07	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	6.97	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	7.92	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	7.23	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	6.96	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	7.19	mg/dL	0.72	1.25	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	12.35	mg/dL	0.66	1.25	.	Clinically significant for concomitant disease
	Day 0	2019-12-11	Yes	12.83	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	14.12	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	12.71	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	12.07	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	11.80	mg/dL	0.72	1.25	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	8.23	mg/dL	0.52	1.04	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	8.82	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	9.31	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	8.74	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	9.11	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	10.17	mg/dL	0.57	1.11	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	7.24	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	9.96	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	7.58	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	8.04	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	8.04	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	7.55	mg/dL	0.72	1.25	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	6.80	mg/dL	0.66	1.25	.	Not Clinically Significant

Listing 7.2 - Study IP-001-09 : Biochemistry - Creatinine

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	6.54	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	6.63	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	6.29	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	6.72	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	6.74	mg/dL	0.72	1.25	.	Not Clinically Significant
01-007	Screening	2019-11-21	No	8.00	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	9.00	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	8.63	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	10.00	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	10.93	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	11.24	mg/dL	0.72	1.25	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	11.08	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	10.44	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	10.87	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	10.44	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	11.07	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	10.75	mg/dL	0.72	1.25	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	7.07	mg/dL	0.52	1.04	.	Clinically sign. for the pathology under study
	Day 0	2019-12-23	Yes	5.64	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	6.12	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	5.42	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	6.12	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	5.71	mg/dL	0.57	1.11	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	7.85	mg/dL	0.72	1.25	.	Clinically sign. for the pathology under study
	Day 0	2020-01-08	Yes	8.26	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	6.25	mg/dL	0.57	1.11	.	Clinically sign. for the pathology under study
	Day 0	2020-03-05	Yes	5.65	mg/dL	0.57	1.11	.	Not Clinically Significant

Listing 7.2 - Study IP-001-09 : Biochemistry - Creatinine

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	5.65	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	6.25	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	6.83	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	6.42	mg/dL	0.57	1.11	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	6.57	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	7.76	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	7.62	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	7.39	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	7.28	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	8.41	mg/dL	0.67	1.17	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	7.78	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	7.98	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	8.36	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	8.87	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	8.38	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	8.02	mg/dL	0.67	1.17	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	10.00	mg/dL	0.67	1.17	.	Clinically significant for concomitant disease
06-002	Screening	2021-12-15	Yes	8.40	mg/dL	0.67	1.17	.	Clinically significant for concomitant disease

Listing 7.3 - Study IP-001-09 : Biochemistry - Glucose

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	90	mg/dL	74	106	.	Normal
	Day 0	2019-11-13	Yes	89	mg/dL	74	106	.	Normal
	Day 14	2019-11-28	Yes	98	mg/dL	74	106	.	Normal
	Day 28	2019-12-12	Yes	92	mg/dL	80	115	.	Normal
	Day 42	2019-12-23	Yes	109	mg/dL	80	115	.	Normal
	Day 56	2020-01-07	Yes	130	mg/dL	80	115	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	148	mg/dL	74	106	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	138	mg/dL	80	115	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	136	mg/dL	80	115	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	222	mg/dL	80	115	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	113	mg/dL	80	115	.	Normal
	Day 56	2020-02-05	Yes	193	mg/dL	80	115	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	87	mg/dL	74	106	.	Normal
	Day 0	2019-12-11	Yes	87	mg/dl	70	105	.	Normal
	Day 14	2019-12-27	Yes	82	mg/dl	70	105	.	Normal
	Day 28	2020-01-10	Yes	124	mg/dl	70	105	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	86	mg/dl	70	105	.	Normal
	Day 56	2020-02-05	Yes	126	mg/dl	70	105	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	104	mg/dL	74	106	.	Normal
	Day 0	2019-12-13	Yes	148	mg/dL	71	99	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	98	mg/dL	71	99	.	Normal
	Day 28	2020-01-09	Yes	107	mg/dL	71	99	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	95	mg/dL	71	99	.	Normal
	Day 56	2020-02-10	Yes	130	mg/dL	71	99	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	131	mg/dL	74	106	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	131	mg/dL	80	115	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	112	mg/dL	80	115	.	Normal
	Day 28	2020-01-10	Yes	166	mg/dL	80	115	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	167	mg/dL	80	115	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	109	mg/dL	80	115	.	Normal
01-006	Screening	2019-11-20	Yes	82	mg/dL	74	106	.	Normal

Listing 7.3 - Study IP-001-09 : Biochemistry - Glucose

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	71	mg/dL	80	115	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	73	mg/dL	80	115	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	113	mg/dL	80	115	.	Normal
	Day 42	2020-01-29	Yes	85	mg/dL	80	115	.	Normal
	Day 56	2020-02-12	Yes	112	mg/dL	80	115	.	Normal
01-007	Screening	2019-11-21	No	199	mg/dL	74	106	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	127	mg/dL	80	115	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	95	mg/dL	80	115	.	Normal
	Day 28	2020-01-16	Yes	115	mg/dL	80	115	.	Normal
	Day 42	2020-01-30	Yes	105	mg/dL	80	115	.	Normal
	Day 56	2020-02-13	Yes	89	mg/dL	80	115	.	Normal
01-008	Screening	2019-11-21	Yes	88	mg/dL	74	106	.	Normal
	Day 0	2019-12-19	Yes	141	mg/dl	70	105	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	90	mg/dl	70	105	.	Normal
	Day 28	2020-01-16	Yes	122	mg/dl	70	105	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	100	mg/dl	70	105	.	Normal
	Day 56	2020-02-13	Yes	83	mg/dl	70	105	.	Normal
01-009	Screening	2019-11-26	Yes	93	mg/dL	74	106	.	Normal
	Day 0	2019-12-23	Yes	94	mg/dL	71	99	.	Normal
	Day 14	2020-01-07	Yes	98	mg/dL	71	99	.	Normal
	Day 28	2020-01-21	Yes	108	mg/dL	71	99	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	86	mg/dL	71	99	.	Normal
	Day 56	2020-02-18	Yes	93	mg/dL	71	99	.	Normal
01-010	Screening	2019-12-12	Yes	78	mg/dL	80	115	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	98	mg/dL	80	115	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	75	mg/dL	71	99	.	Normal
	Day 0	2020-03-05	Yes	78	mg/dL	71	99	.	Normal

Listing 7.3 - Study IP-001-09 : Biochemistry - Glucose

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	84	mg/dL	71	99	.	Normal
	Day 28	2020-04-02	Yes	83	mg/dL	71	99	.	Normal
	Day 42	2020-04-16	Yes	78	mg/dL	71	99	.	Normal
	Day 56	2020-04-30	Yes	136	mg/dL	71	99	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	100	mg/dL	0	100	.	Normal
	Day 0	2021-11-10	Yes	95	mg/dL	0	100	.	Normal
	Day 14	2021-11-26	Yes	93	mg/dL	0	100	.	Normal
	Day 28	2021-12-09	Yes	101	mg/dL	0	100	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	108	mg/dL	0	100	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	107	mg/dL	0	100	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	155	mg/dL	0	100	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	137	mg/dL	0	100	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	127	mg/dL	0	100	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	179	mg/dL	0	100	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	147	mg/dL	0	100	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	88	mg/dL	0	100	.	Normal
06-001	Screening	2021-12-15	Yes	60	mg/dL	65	100	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	73	mg/dL	65	100	.	Not Clinically Significant

Listing 7.4 - Study IP-001-09 : Biochemistry - Total Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-001	Screening	2019-10-16	Yes	.	mg/dl	0	200	Yes		.
	Day 0	2019-11-13	Yes	149	mg/dl	0	200	.	Normal	
	Day 14	2019-11-28	Yes	150	mg/dl	0	200	.	Normal	
	Day 28	2019-12-12	Yes	135	mg/dl	0	200	.	Normal	
	Day 42	2019-12-23	Yes	153	mg/dl	0	200	.	Normal	
	Day 56	2020-01-07	Yes	.	mg/dl	0	200	Yes		.
01-002	Screening	2019-11-13	Yes	123	mg/dl	0	200	.	Normal	
	Day 0	2019-12-11	Yes	113	mg/dl	0	200	.	Normal	
	Day 14	2019-12-27	Yes	121	mg/dl	0	200	.	Normal	
	Day 28	2020-01-08	Yes	123	mg/dl	0	200	.	Normal	
	Day 42	2020-01-22	Yes	117	mg/dl	0	200	.	Normal	
	Day 56	2020-02-05	Yes	120	mg/dl	0	200	.	Normal	
01-003	Screening	2019-11-13	Yes	147	mg/dl	0	200	.	Normal	
	Day 0	2019-12-11	Yes	134	mg/dl	0	200	.	Normal	
	Day 14	2019-12-27	Yes	141	mg/dl	0	200	.	Normal	
	Day 28	2020-01-10	Yes	142	mg/dl	0	200	.	Normal	
	Day 42	2020-01-22	Yes	141	mg/dl	0	200	.	Normal	
	Day 56	2020-02-05	Yes	158	mg/dl	0	200	.	Normal	
01-004	Screening	2019-11-15	Yes	143	mg/dl	0	200	.	Normal	
	Day 0	2019-12-13	Yes	143	mg/dl	0	200	.	Normal	
	Day 14	2019-12-27	Yes	147	mg/dl	0	200	.	Normal	
	Day 28	2020-01-09	Yes	141	mg/dl	0	200	.	Normal	
	Day 42	2020-01-23	Yes	144	mg/dl	0	200	.	Normal	
	Day 56	2020-02-10	Yes	144	mg/dl	0	200	.	Normal	
01-005	Screening	2019-11-15	Yes	231	mg/dl	0	200	.	Not Clinically Significant	
	Day 0	2019-12-13	Yes	163	mg/dl	0	200	.	Normal	
	Day 14	2019-12-27	Yes	186	mg/dl	0	200	.	Normal	
	Day 28	2020-01-10	Yes	245	mg/dl	0	200	.	Not Clinically Significant	
	Day 42	2020-01-24	Yes	277	mg/dl	0	200	.	Not Clinically Significant	
	Day 56	2020-02-07	Yes	236	mg/dl	0	200	.	Not Clinically Significant	
01-006	Screening	2019-11-20	Yes	175	mg/dl	0	200	.	Normal	

Listing 7.4 - Study IP-001-09 : Biochemistry - Total Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	182	mg/dl	0	200	.	Normal	
	Day 14	2020-01-03	Yes	220	mg/dl	0	200	.	Not Clinically Significant	
	Day 28	2020-01-15	Yes	194	mg/dl	0	200	.	Normal	
	Day 42	2020-01-29	Yes	185	mg/dl	0	200	.	Normal	
	Day 56	2020-02-12	Yes	193	mg/dl	0	200	.	Normal	
01-007	Screening	2019-11-21	No	237	mg/dl	0	200	.	Not Clinically Significant	
	Day 0	2019-12-19	Yes	180	mg/dl	0	200	.	Normal	
	Day 14	2020-01-03	Yes	199	mg/dl	0	200	.	Normal	
	Day 28	2020-01-16	Yes	136	mg/dl	0	200	.	Normal	
	Day 42	2020-01-30	Yes	157	mg/dl	0	200	.	Normal	
	Day 56	2020-02-13	Yes	134	mg/dl	0	200	.	Normal	
01-008	Screening	2019-11-21	Yes	138	mg/dl	0	200	.	Normal	
	Day 0	2019-12-19	Yes	133	mg/dl	0	200	.	Normal	
	Day 14	2020-01-03	Yes	131	mg/dl	0	200	.	Normal	
	Day 28	2020-01-16	Yes	133	mg/dl	0	200	.	Normal	
	Day 42	2020-01-30	Yes	133	mg/dl	0	200	.	Normal	
	Day 56	2020-02-13	Yes	125	mg/dl	0	200	.	Normal	
01-009	Screening	2019-11-26	Yes	172	mg/dl	0	200	.	Normal	
	Day 0	2019-12-23	Yes	196	mg/dl	0	200	.	Normal	
	Day 14	2020-01-07	Yes	191	mg/dl	0	200	.	Normal	
	Day 28	2020-01-21	Yes	183	mg/dl	0	200	.	Normal	
	Day 42	2020-02-04	Yes	198	mg/dl	0	200	.	Normal	
	Day 56	2020-02-18	Yes	198	mg/dl	0	200	.	Normal	
01-010	Screening	2019-12-12	Yes	108	mg/dl	0	200	.	Normal	
	Day 0	2020-01-08	Yes	102	mg/dl	0	200	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	161	mg/dl	0	200	.	Normal	
	Day 0	2020-03-05	Yes	166	mg/dl	0	200	.	Normal	

Listing 7.4 - Study IP-001-09 : Biochemistry - Total Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	145	mg/dl	0	200	.	Normal
	Day 28	2020-04-02	Yes	157	mg/dl	0	200	.	Normal
	Day 42	2020-04-16	Yes	174	mg/dl	0	200	.	Normal
	Day 56	2020-04-30	Yes	152	mg/dl	0	200	.	Normal
05-001	Screening	2021-10-13	No	185	mg/dL	0	200	.	Normal
	Day 0	2021-11-10	Yes	156	mg/dL	0	200	.	Normal
	Day 14	2021-11-26	Yes	172	mg/dL	0	200	.	Normal
	Day 28	2021-12-09	Yes	161	mg/dL	0	200	.	Normal
	Day 42	2022-01-28	Yes	178	mg/dL	0	200	.	Normal
	Day 56	2022-02-22	Yes	191	mg/dL	0	200	.	Normal
05-002	Screening	2021-10-29	Yes	157	mg/dL	0	200	.	Normal
	Day 0	2021-11-30	Yes	142	mg/dL	0	200	.	Normal
	Day 14	2021-12-14	Yes	113	mg/dL	0	200	.	Normal
	Day 28	2021-12-30	Yes	109	mg/dL	0	200	.	Normal
	Day 42	2022-01-15	Yes	128	mg/dL	0	200	.	Normal
	Day 56	2022-02-03	Yes	110	mg/dL	0	200	.	Normal
06-001	Screening	2021-12-15	Yes	130	mg/dL	130	200	.	Normal
06-002	Screening	2021-12-15	Yes	160	mg/dL	130	200	.	Not Clinically Significant

Listing 7.5 - Study IP-001-09 : Biochemistry - HDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-001	Screening	2019-10-16	Yes	.	mg/dl	40	60	Yes		.
	Day 0	2019-11-13	Yes	49	mg/dl	40	60	.	Normal	
	Day 14	2019-11-28	Yes	54	mg/dl	40	60	.	Normal	
	Day 28	2019-12-12	Yes	47	mg/dl	40	60	.	Normal	
	Day 42	2019-12-23	Yes	52	mg/dl	40	60	.	Normal	
	Day 56	2020-01-07	Yes	.	mg/dl	40	60	Yes		.
01-002	Screening	2019-11-13	Yes	37	mg/dl	40	60	.	Not Clinically Significant	
	Day 0	2019-12-11	Yes	39	mg/dl	40	60	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	38	mg/dl	40	60	.	Not Clinically Significant	
	Day 28	2020-01-08	Yes	40	mg/dl	40	60	.	Normal	
	Day 42	2020-01-22	Yes	35	mg/dl	40	60	.	Not Clinically Significant	
	Day 56	2020-02-05	Yes	38	mg/dl	40	60	.	Not Clinically Significant	
01-003	Screening	2019-11-13	Yes	26	mg/dl	40	60	.	Not Clinically Significant	
	Day 0	2019-12-11	Yes	25	mg/dl	40	60	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	29	mg/dl	40	60	.	Not Clinically Significant	
	Day 28	2020-01-10	Yes	31	mg/dl	40	60	.	Not Clinically Significant	
	Day 42	2020-01-22	Yes	30	mg/dl	40	60	.	Not Clinically Significant	
	Day 56	2020-02-05	Yes	33	mg/dl	40	60	.	Not Clinically Significant	
01-004	Screening	2019-11-15	Yes	48	mg/dl	40	60	.	Normal	
	Day 0	2019-12-13	Yes	52	mg/dl	40	60	.	Normal	
	Day 14	2019-12-27	Yes	50	mg/dl	40	60	.	Normal	
	Day 28	2020-01-09	Yes	56	mg/dl	40	60	.	Normal	
	Day 42	2020-01-23	Yes	51	mg/dl	40	60	.	Normal	
	Day 56	2020-02-10	Yes	48	mg/dl	40	60	.	Normal	
01-005	Screening	2019-11-15	Yes	30	mg/dl	40	60	.	Not Clinically Significant	
	Day 0	2019-12-13	Yes	27	mg/dl	40	60	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	28	mg/dl	40	60	.	Not Clinically Significant	
	Day 28	2020-01-10	Yes	27	mg/dl	40	60	.	Not Clinically Significant	
	Day 42	2020-01-24	Yes	28	mg/dl	40	60	.	Not Clinically Significant	
	Day 56	2020-02-07	Yes	26	mg/dl	40	60	.	Not Clinically Significant	
01-006	Screening	2019-11-20	Yes	25	mg/dl	40	60	.	Not Clinically Significant	

Listing 7.5 - Study IP-001-09 : Biochemistry - HDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	25	mg/dl	40	60	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	32	mg/dl	40	60	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	31	mg/dl	40	60	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	30	mg/dl	40	60	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	31	mg/dl	40	60	.	Not Clinically Significant
01-007	Screening	2019-11-21	No	32	mg/dl	40	60	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	34	mg/dl	40	60	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	31	mg/dl	40	60	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	29	mg/dl	40	60	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	25	mg/dl	40	60	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	26	mg/dl	40	60	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	46	mg/dl	40	60	.	Normal
	Day 0	2019-12-19	Yes	42	mg/dl	40	60	.	Normal
	Day 14	2020-01-03	Yes	36	mg/dl	40	60	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	45	mg/dl	40	60	.	Normal
	Day 42	2020-01-30	Yes	35	mg/dl	40	60	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	35	mg/dl	40	60	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	33	mg/dl	40	60	.	Not Clinically Significant
	Day 0	2019-12-23	Yes	35	mg/dl	40	60	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	38	mg/dl	40	60	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	37	mg/dl	40	60	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	43	mg/dl	40	60	.	Normal
	Day 56	2020-02-18	Yes	39	mg/dl	40	60	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	32	mg/dl	40	60	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	36	mg/dl	40	60	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	44	mg/dl	40	60	.	Normal
	Day 0	2020-03-05	Yes	50	mg/dl	40	60	.	Normal

Listing 7.5 - Study IP-001-09 : Biochemistry - HDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-011	Day 14	2020-03-20	Yes	38	mg/dl	40	60	.	Not Clinically Significant	
	Day 28	2020-04-02	Yes	41	mg/dl	40	60	.	Normal	
	Day 42	2020-04-16	Yes	46	mg/dl	40	60	.	Normal	
	Day 56	2020-04-30	Yes	41	mg/dl	40	60	.	Normal	
05-001	Screening	2021-10-13	No	.	mg/dL	40	200	Yes		.
	Day 0	2021-11-10	Yes	49	mg/dL	40	200	.	Normal	
	Day 14	2021-11-26	Yes	46	mg/dL	40	200	.	Normal	
	Day 28	2021-12-09	Yes	49	mg/dL	40	200	.	Normal	
	Day 42	2022-01-28	Yes	57	mg/dL	40	200	.	Normal	
	Day 56	2022-02-22	Yes	42	mg/dL	40	200	.	Normal	
05-002	Screening	2021-10-29	Yes	75	mg/dL	40	200	.	Normal	
	Day 0	2021-11-30	Yes	78	mg/dL	40	200	.	Normal	
	Day 14	2021-12-14	Yes	54	mg/dL	40	200	.	Normal	
	Day 28	2021-12-30	Yes	47	mg/dL	40	200	.	Normal	
	Day 42	2022-01-15	Yes	56	mg/dL	40	200	.	Normal	
	Day 56	2022-02-03	Yes	49	mg/dL	40	200	.	Normal	
06-001	Screening	2021-12-15	Yes	44	mg/dL	45	200	.	Not Clinically Significant	
06-002	Screening	2021-12-15	Yes	102	mg/dL	45	200	.	Not Clinically Significant	

Listing 7.6 - Study IP-001-09 : Biochemistry - LDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-001	Screening	2019-10-16	Yes	.	mg/dL	0	150	Yes		.
	Day 0	2019-11-13	Yes	72.0	mg/dL	0	150	.	Normal	
	Day 14	2019-11-28	Yes	69.0	mg/dL	0	150	.	Normal	
	Day 28	2019-12-12	Yes	70.0	mg/dL	0	100	.	Normal	
	Day 42	2019-12-23	Yes	84.0	mg/dL	0	100	.	Normal	
	Day 56	2020-01-07	Yes	.	mg/dL	0	100	Yes		.
01-002	Screening	2019-11-13	Yes	69.2	mg/dL	0	150	.	Normal	
	Day 0	2019-12-11	Yes	56.0	mg/dL	0	100	.	Normal	
	Day 14	2019-12-27	Yes	67.0	mg/dL	0	100	.	Normal	
	Day 28	2020-01-08	Yes	61.0	mg/dL	0	100	.	Normal	
	Day 42	2020-01-22	Yes	65.0	mg/dL	0	100	.	Normal	
	Day 56	2020-02-05	Yes	60.0	mg/dL	0	100	.	Normal	
01-003	Screening	2019-11-13	Yes	54.8	mg/dL	0	150	.	Normal	
	Day 0	2019-12-11	Yes	75.0	mg/dL	0	100	.	Normal	
	Day 14	2019-12-27	Yes	72.0	mg/dL	0	100	.	Normal	
	Day 28	2020-01-10	Yes	79.0	mg/dL	0	100	.	Normal	
	Day 42	2020-01-22	Yes	85.0	mg/dL	0	100	.	Normal	
	Day 56	2020-02-05	Yes	83.0	mg/dL	0	100	.	Normal	
01-004	Screening	2019-11-15	Yes	69.2	mg/dL	0	150	.	Normal	
	Day 0	2019-12-13	Yes	70.0	mg/dL	0	100	.	Normal	
	Day 14	2019-12-27	Yes	67.0	mg/dL	0	100	.	Normal	
	Day 28	2020-01-09	Yes	63.0	mg/dL	0	100	.	Normal	
	Day 42	2020-01-23	Yes	85.0	mg/dL	0	100	.	Normal	
	Day 56	2020-02-10	Yes	67.0	mg/dL	0	100	.	Normal	
01-005	Screening	2019-11-15	Yes	149.0	mg/dL	0	150	.	Normal	
	Day 0	2019-12-13	Yes	104.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	117.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 28	2020-01-10	Yes	133.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 42	2020-01-24	Yes	157.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 56	2020-02-07	Yes	141.0	mg/dL	0	100	.	Not Clinically Significant	
01-006	Screening	2019-11-20	Yes	97.8	mg/dL	0	150	.	Normal	

Listing 7.6 - Study IP-001-09 : Biochemistry - LDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	105.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 14	2020-01-03	Yes	98.0	mg/dL	0	100	.	Normal	
	Day 28	2020-01-15	Yes	97.0	mg/dL	0	100	.	Normal	
	Day 42	2020-01-29	Yes	121.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 56	2020-02-12	Yes	113.0	mg/dL	0	100	.	Not Clinically Significant	
01-007	Screening	2019-11-21	No	100.8	mg/dL	0	150	.	Normal	
	Day 0	2019-12-19	Yes	97.0	mg/dL	0	100	.	Normal	
	Day 14	2020-01-03	Yes	76.0	mg/dL	0	100	.	Normal	
	Day 28	2020-01-16	Yes	75.0	mg/dL	0	100	.	Normal	
	Day 42	2020-01-30	Yes	72.0	mg/dL	0	100	.	Normal	
	Day 56	2020-02-13	Yes	79.0	mg/dL	0	100	.	Normal	
01-008	Screening	2019-11-21	Yes	75.2	mg/dL	0	150	.	Normal	
	Day 0	2019-12-19	Yes	73.0	mg/dL	0	100	.	Normal	
	Day 14	2020-01-03	Yes	72.0	mg/dL	0	100	.	Normal	
	Day 28	2020-01-16	Yes	68.0	mg/dL	0	100	.	Normal	
	Day 42	2020-01-30	Yes	69.0	mg/dL	0	100	.	Normal	
	Day 56	2020-02-13	Yes	70.0	mg/dL	0	100	.	Normal	
01-009	Screening	2019-11-26	Yes	91.4	mg/dL	0	150	.	Normal	
	Day 0	2019-12-23	Yes	114.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 14	2020-01-07	Yes	117.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 28	2020-01-21	Yes	109.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 42	2020-02-04	Yes	126.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 56	2020-02-18	Yes	126.0	mg/dL	0	100	.	Not Clinically Significant	
01-010	Screening	2019-12-12	Yes	59.4	mg/dL	0	100	.	Normal	
	Day 0	2020-01-08	Yes	50.0	mg/dL	0	100	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	95.0	mg/dL	0	100	.	Normal	
	Day 0	2020-03-05	Yes	91.0	mg/dL	0	100	.	Normal	

Listing 7.6 - Study IP-001-09 : Biochemistry - LDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-011	Day 14	2020-03-20	Yes	70.0	mg/dL	0	100	.	Normal	
	Day 28	2020-04-02	Yes	85.0	mg/dL	0	100	.	Normal	
	Day 42	2020-04-16	Yes	96.0	mg/dL	0	100	.	Normal	
	Day 56	2020-04-30	Yes	79.0	mg/dL	0	100	.	Normal	
05-001	Screening	2021-10-13	No	.	mg/dL	0	70	Yes		.
	Day 0	2021-11-10	Yes	72.0	mg/dL	0	70	.	Not Clinically Significant	
	Day 14	2021-11-26	Yes	77.0	mg/dL	0	70	.	Not Clinically Significant	
	Day 28	2021-12-09	Yes	69.0	mg/dL	0	70	.	Normal	
	Day 42	2022-01-28	Yes	91.0	mg/dL	0	70	.	Not Clinically Significant	
	Day 56	2022-02-22	Yes	108.0	mg/dL	0	70	.	Not Clinically Significant	
05-002	Screening	2021-10-29	Yes	60.0	mg/dL	0	70	.	Normal	
	Day 0	2021-11-30	Yes	47.0	mg/dL	0	70	.	Normal	
	Day 14	2021-12-14	Yes	37.0	mg/dL	0	70	.	Normal	
	Day 28	2021-12-30	Yes	43.0	mg/dL	0	70	.	Normal	
	Day 42	2022-01-15	Yes	51.0	mg/dL	0	70	.	Normal	
	Day 56	2022-02-03	Yes	47.0	mg/dL	0	70	.	Normal	
06-001	Screening	2021-12-15	Yes	73.0	mg/dL	0	130	.	Normal	
06-002	Screening	2021-12-15	Yes	47.0	mg/dL	0	130	.	Not Clinically Significant	

Listing 7.7 - Study IP-001-09 : Biochemistry - Triglycerides

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-001	Screening	2019-10-16	Yes	.	mg/dl	70	200	Yes		.
	Day 0	2019-11-13	Yes	144	mg/dl	70	200	.	Normal	
	Day 14	2019-11-28	Yes	.	mg/dl	70	200	Yes		.
	Day 28	2019-12-12	Yes	102	mg/dL	0	150	.	Normal	
	Day 42	2019-12-23	Yes	85	mg/dL	0	150	.	Normal	
	Day 56	2020-01-07	Yes	74	mg/dL	0	150	.	Normal	
01-002	Screening	2019-11-13	Yes	84	mg/dl	70	200	.	Normal	
	Day 0	2019-12-11	Yes	77	mg/dL	0	150	.	Normal	
	Day 14	2019-12-27	Yes	66	mg/dL	0	150	.	Normal	
	Day 28	2020-01-08	Yes	97	mg/dL	0	150	.	Normal	
	Day 42	2020-01-22	Yes	67	mg/dL	0	150	.	Normal	
	Day 56	2020-02-05	Yes	76	mg/dL	0	150	.	Normal	
01-003	Screening	2019-11-13	Yes	331	mg/dl	70	200	.	Not Clinically Significant	
	Day 0	2019-12-11	Yes	189	mg/dL	0	150	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	219	mg/dL	0	150	.	Not Clinically Significant	
	Day 28	2020-01-10	Yes	179	mg/dL	0	150	.	Not Clinically Significant	
	Day 42	2020-01-22	Yes	137	mg/dL	0	150	.	Normal	
	Day 56	2020-02-05	Yes	171	mg/dL	0	150	.	Not Clinically Significant	
01-004	Screening	2019-11-15	Yes	129	mg/dl	70	200	.	Normal	
	Day 0	2019-12-13	Yes	106	mg/dL	0	150	.	Normal	
	Day 14	2019-12-27	Yes	141	mg/dL	0	150	.	Normal	
	Day 28	2020-01-09	Yes	107	mg/dL	0	150	.	Normal	
	Day 42	2020-01-23	Yes	80	mg/dL	0	150	.	Normal	
	Day 56	2020-02-10	Yes	122	mg/dL	0	150	.	Normal	
01-005	Screening	2019-11-15	Yes	260	mg/dl	70	200	.	Not Clinically Significant	
	Day 0	2019-12-13	Yes	131	mg/dL	0	150	.	Normal	
	Day 14	2019-12-27	Yes	169	mg/dL	0	150	.	Not Clinically Significant	
	Day 28	2020-01-10	Yes	.	mg/dL	0	150	Yes		.
	Day 42	2020-01-24	Yes	336	mg/dL	0	150	.	Not Clinically Significant	
	Day 56	2020-02-07	Yes	250	mg/dL	0	150	.	Not Clinically Significant	
01-006	Screening	2019-11-20	Yes	261	mg/dl	70	200	.	Not Clinically Significant	

Listing 7.7 - Study IP-001-09 : Biochemistry - Triglycerides

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	.	mg/dL	0	150	Yes		.
	Day 14	2020-01-03	Yes	319	mg/dL	0	150	.	Not Clinically Significant	
	Day 28	2020-01-15	Yes	257	mg/dL	0	150	.	Not Clinically Significant	
	Day 42	2020-01-29	Yes	165	mg/dL	0	150	.	Not Clinically Significant	
	Day 56	2020-02-12	Yes	178	mg/dL	0	150	.	Not Clinically Significant	
01-007	Screening	2019-11-21	No	521	mg/dl	70	200	.	Not Clinically Significant	
	Day 0	2019-12-19	Yes	364	mg/dL	0	150	.	Not Clinically Significant	
	Day 14	2020-01-03	Yes	808	mg/dL	0	150	.	Not Clinically Significant	
	Day 28	2020-01-16	Yes	344	mg/dL	0	150	.	Not Clinically Significant	
	Day 42	2020-01-30	Yes	300	mg/dL	0	150	.	Not Clinically Significant	
	Day 56	2020-02-13	Yes	174	mg/dL	0	150	.	Not Clinically Significant	
01-008	Screening	2019-11-21	Yes	84	mg/dl	70	200	.	Normal	
	Day 0	2019-12-19	Yes	101	mg/dL	0	150	.	Normal	
	Day 14	2020-01-03	Yes	112	mg/dL	0	150	.	Normal	
	Day 28	2020-01-16	Yes	100	mg/dL	0	150	.	Normal	
	Day 42	2020-01-30	Yes	102	mg/dL	0	150	.	Normal	
	Day 56	2020-02-13	Yes	125	mg/dL	0	150	.	Normal	
01-009	Screening	2019-11-26	Yes	238	mg/dl	70	200	.	Not Clinically Significant	
	Day 0	2019-12-23	Yes	85	mg/dL	0	150	.	Normal	
	Day 14	2020-01-07	Yes	130	mg/dL	0	150	.	Normal	
	Day 28	2020-01-21	Yes	128	mg/dL	0	150	.	Normal	
	Day 42	2020-02-04	Yes	132	mg/dL	0	150	.	Normal	
	Day 56	2020-02-18	Yes	146	mg/dL	0	150	.	Normal	
01-010	Screening	2019-12-12	Yes	83	mg/dL	0	150	.	Normal	
	Day 0	2020-01-08	Yes	83	mg/dL	0	150	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	122	mg/dL	0	150	.	Normal	
	Day 0	2020-03-05	Yes	151	mg/dL	0	150	.	Not Clinically Significant	

Listing 7.7 - Study IP-001-09 : Biochemistry - Triglycerides

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	187	mg/dL	0	150	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	154	mg/dL	0	150	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	171	mg/dL	0	150	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	155	mg/dL	0	150	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	205	mg/dL	0	150	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	177	mg/dL	0	150	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	244	mg/dL	0	150	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	217	mg/dL	0	150	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	151	mg/dL	0	150	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	203	mg/dL	0	150	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	108	mg/dL	0	150	.	Normal
	Day 0	2021-11-30	Yes	84	mg/dL	0	150	.	Normal
	Day 14	2021-12-14	Yes	108	mg/dL	0	150	.	Normal
	Day 28	2021-12-30	Yes	97	mg/dL	0	150	.	Normal
	Day 42	2022-01-15	Yes	104	mg/dL	0	150	.	Normal
	Day 56	2022-02-03	Yes	69	mg/dL	0	150	.	Normal
06-001	Screening	2021-12-15	Yes	65	mg/dL	20	170	.	Normal
06-002	Screening	2021-12-15	Yes	55	mg/dL	20	170	.	Not Clinically Significant

Listing 7.8 - Study IP-001-09 : Biochemistry - Total proteins

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	6.2	g/dl	6.3	8.2	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	6.3	g/dl	6.3	8.2	.	Normal
	Day 14	2019-11-28	Yes	6.6	g/dl	6.3	8.2	.	Normal
	Day 28	2019-12-12	Yes	5.9	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	6.4	md/dL	6.4	8.3	.	Normal
	Day 56	2020-01-07	Yes	6.1	md/dL	6.4	8.3	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	6.3	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-11	Yes	5.9	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	5.8	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	6.1	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	5.8	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	5.5	md/dL	6.4	8.3	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	6.0	g/dl	6.3	8.2	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	5.6	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	5.8	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	5.6	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	5.4	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	5.2	md/dL	6.4	8.3	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	6.4	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-13	Yes	5.9	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	6.3	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	6.5	mg/dL	6.4	8.3	.	Normal
	Day 42	2020-01-23	Yes	6.1	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	6.5	mg/dL	6.4	8.3	.	Normal
01-005	Screening	2019-11-15	Yes	7.5	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-13	Yes	6.5	md/dL	6.4	8.3	.	Normal
	Day 14	2019-12-27	Yes	6.5	md/dL	6.4	8.3	.	Normal
	Day 28	2020-01-10	Yes	6.7	md/dL	6.4	8.3	.	Normal
	Day 42	2020-01-24	Yes	7.1	md/dL	6.4	8.3	.	Normal
	Day 56	2020-02-07	Yes	6.7	md/dL	6.4	8.3	.	Normal
01-006	Screening	2019-11-20	Yes	7.1	g/dl	6.3	8.2	.	Normal

Listing 7.8 - Study IP-001-09 : Biochemistry - Total proteins

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	6.7	md/dL	6.4	8.3	.	Normal
	Day 14	2020-01-03	Yes	6.8	md/dL	6.4	8.3	.	Normal
	Day 28	2020-01-15	Yes	6.6	md/dL	6.4	8.3	.	Normal
	Day 42	2020-01-29	Yes	6.7	md/dL	6.4	8.3	.	Normal
	Day 56	2020-02-12	Yes	6.8	md/dL	6.4	8.3	.	Normal
01-007	Screening	2019-11-21	No	7.1	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-19	Yes	7.3	md/dL	6.4	8.3	.	Normal
	Day 14	2020-01-03	Yes	7.3	md/dL	6.4	8.3	.	Normal
	Day 28	2020-01-16	Yes	6.9	md/dL	6.4	8.3	.	Normal
	Day 42	2020-01-30	Yes	6.7	md/dL	6.4	8.3	.	Normal
	Day 56	2020-02-13	Yes	6.7	md/dL	6.4	8.3	.	Normal
01-008	Screening	2019-11-21	Yes	6.8	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-19	Yes	6.7	md/dL	6.4	8.3	.	Normal
	Day 14	2020-01-03	Yes	6.9	md/dL	6.4	8.3	.	Normal
	Day 28	2020-01-16	Yes	6.6	md/dL	6.4	8.3	.	Normal
	Day 42	2020-01-30	Yes	6.6	md/dL	6.4	8.3	.	Normal
	Day 56	2020-02-13	Yes	6.8	md/dL	6.4	8.3	.	Normal
01-009	Screening	2019-11-26	Yes	6.4	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-23	Yes	5.9	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	6.1	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	5.9	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	5.9	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	6.3	mg/dL	6.4	8.3	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	6.2	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	6.5	md/dL	6.4	8.3	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	6.1	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 0	2020-03-05	Yes	6.9	mg/dL	6.4	8.3	.	Normal

Listing 7.8 - Study IP-001-09 : Biochemistry - Total proteins

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	6.6	mg/dL	6.4	8.3	.	Normal
	Day 28	2020-04-02	Yes	6.7	mg/dL	6.4	8.3	.	Normal
	Day 42	2020-04-16	Yes	6.6	mg/dL	6.4	8.3	.	Normal
	Day 56	2020-04-30	Yes	6.6	mg/dL	6.4	8.3	.	Normal
05-001	Screening	2021-10-13	No	5.7	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	5.5	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	5.6	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	5.4	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	5.5	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	5.8	g/dL	6.4	8.2	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	6.2	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	6.6	g/dL	6.4	8.2	.	Normal
	Day 14	2021-12-14	Yes	6.5	g/dL	6.4	8.2	.	Normal
	Day 28	2021-12-30	Yes	6.5	g/dL	6.4	8.2	.	Normal
	Day 42	2022-01-15	Yes	7.1	g/dL	6.4	8.2	.	Normal
	Day 56	2022-02-03	Yes	6.3	g/dL	6.4	8.2	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	60.0	g/L	65.0	85.0	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	69.0	g/L	65.0	85.0	.	Not Clinically Significant

Listing 7.9 - Study IP-001-09 : Biochemistry - Albumin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 0	2019-11-13	Yes	3.50	g/dl	3.5	5.2	.	Normal
	Day 14	2019-11-28	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 28	2019-12-12	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 42	2019-12-23	Yes	4.00	g/dl	3.5	5.2	.	Normal
	Day 56	2020-01-07	Yes	3.90	g/dl	3.5	5.2	.	Normal
01-002	Screening	2019-11-13	Yes	3.93	g/dl	3.5	5.2	.	Normal
	Day 0	2019-12-11	Yes	3.74	g/dl	3.5	5.2	.	Normal
	Day 14	2019-12-27	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-08	Yes	4.00	g/dl	3.5	5.2	.	Normal
	Day 42	2020-01-22	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-05	Yes	3.70	g/dl	3.5	5.2	.	Normal
01-003	Screening	2019-11-13	Yes	3.81	g/dl	3.5	5.2	.	Normal
	Day 0	2019-12-11	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 14	2019-12-27	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-10	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 42	2020-01-22	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-05	Yes	3.50	g/dl	3.5	5.2	.	Normal
01-004	Screening	2019-11-15	Yes	3.85	g/dl	3.5	5.2	.	Normal
	Day 0	2019-12-13	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 14	2019-12-27	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-09	Yes	4.00	g/dl	3.5	5.2	.	Normal
	Day 42	2020-01-23	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-10	Yes	4.00	g/dl	3.5	5.2	.	Normal
01-005	Screening	2019-11-15	Yes	4.01	g/dl	3.5	5.2	.	Normal
	Day 0	2019-12-13	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 14	2019-12-27	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-10	Yes	0.25	g/dl	3.5	5.2	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	3.90	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-07	Yes	3.80	g/dl	3.5	5.2	.	Normal
01-006	Screening	2019-11-20	Yes	3.97	g/dl	3.5	5.2	.	Normal

Listing 7.9 - Study IP-001-09 : Biochemistry - Albumin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	3.60	g/dl	3.5	5.2	.	Normal	
	Day 14	2020-01-03	Yes	3.80	g/dl	3.5	5.2	.	Normal	
	Day 28	2020-01-15	Yes	3.80	g/dl	3.5	5.2	.	Normal	
	Day 42	2020-01-29	Yes	3.80	g/dl	3.5	5.2	.	Normal	
	Day 56	2020-02-12	Yes	3.90	g/dl	3.5	5.2	.	Normal	
01-007	Screening	2019-11-21	No	4.09	g/dl	3.5	5.2	.	Normal	
	Day 0	2019-12-19	Yes	4.00	g/dl	3.5	5.2	.	Normal	
	Day 14	2020-01-03	Yes	4.00	g/dl	3.5	5.2	.	Normal	
	Day 28	2020-01-16	Yes	4.00	g/dl	3.5	5.2	.	Normal	
	Day 42	2020-01-30	Yes	4.00	g/dl	3.5	5.2	.	Normal	
	Day 56	2020-02-13	Yes	3.60	g/dl	3.5	5.2	.	Normal	
01-008	Screening	2019-11-21	Yes	4.34	g/dl	3.5	5.2	.	Normal	
	Day 0	2019-12-19	Yes	4.10	g/dl	3.5	5.2	.	Normal	
	Day 14	2020-01-03	Yes	4.10	g/dl	3.5	5.2	.	Normal	
	Day 28	2020-01-16	Yes	4.10	g/dl	3.5	5.2	.	Normal	
	Day 42	2020-01-30	Yes	4.20	g/dl	3.5	5.2	.	Normal	
	Day 56	2020-02-13	Yes	4.00	g/dl	3.5	5.2	.	Normal	
01-009	Screening	2019-11-26	Yes	2.51	g/dl	3.5	5.2	.	Not Clinically Significant	
	Day 0	2019-12-23	Yes	3.70	g/dl	3.5	5.2	.	Normal	
	Day 14	2020-01-07	Yes	3.80	g/dl	3.5	5.2	.	Normal	
	Day 28	2020-01-21	Yes	3.70	g/dl	3.5	5.2	.	Normal	
	Day 42	2020-02-04	Yes	3.80	g/dl	3.5	5.2	.	Normal	
	Day 56	2020-02-18	Yes	3.90	g/dl	3.5	5.2	.	Normal	
01-010	Screening	2019-12-12	Yes	3.31	g/dl	3.5	5.2	.	Not Clinically Significant	
	Day 0	2020-01-08	Yes	3.60	g/dl	3.5	5.2	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	3.50	g/dl	3.5	5.2	.	Normal	
	Day 0	2020-03-05	Yes	3.90	g/dl	3.5	5.2	.	Normal	

Listing 7.9 - Study IP-001-09 : Biochemistry - Albumin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 28	2020-04-02	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 42	2020-04-16	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 56	2020-04-30	Yes	3.80	g/dl	3.5	5.2	.	Normal
05-001	Screening	2021-10-13	No	2.40	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	2.00	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	2.40	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	2.20	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	2.50	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	2.50	g/dL	3.4	5.0	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	3.10	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	3.20	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	3.60	g/dL	3.4	5.0	.	Normal
	Day 28	2021-12-30	Yes	3.40	g/dL	3.4	5.0	.	Normal
	Day 42	2022-01-15	Yes	3.70	g/dL	3.4	5.0	.	Normal
	Day 56	2022-02-03	Yes	3.00	g/dL	3.4	5.0	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	31.00	g/L	34.0	48.0	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	41.00	g/L	34.0	48.0	.	Not Clinically Significant

Listing 7.10 - Study IP-001-09 : Biochemistry - Total bilirubin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done		Evaluation	
01-001	Screening	2019-10-16	Yes	.	mg/dl	0.2	1.3	Yes			.
	Day 0	2019-11-13	Yes	0.86	mg/dl	0.2	1.3	.	Normal		
	Day 14	2019-11-28	Yes	0.77	mg/dl	0.2	1.3	.	Normal		
	Day 28	2019-12-12	Yes	.	mg/dL	0.2	1.2	Yes			.
	Day 42	2019-12-23	Yes	0.83	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-01-07	Yes	0.74	mg/dL	0.2	1.2	.	Normal		
01-002	Screening	2019-11-13	Yes	0.60	mg/dl	0.2	1.3	.	Normal		
	Day 0	2019-12-11	Yes	.	mg/dL	0.2	1.2	Yes			.
	Day 14	2019-12-27	Yes	0.62	mg/dL	0.2	1.2	.	Normal		
	Day 28	2020-01-08	Yes	0.82	mg/dL	0.2	1.2	.	Normal		
	Day 42	2020-01-22	Yes	0.47	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-02-05	Yes	0.44	mg/dL	0.2	1.2	.	Normal		
01-003	Screening	2019-11-13	Yes	0.55	mg/dl	0.2	1.3	.	Normal		
	Day 0	2019-12-11	Yes	0.50	mg/dL	0.2	1.2	.	Normal		
	Day 14	2019-12-27	Yes	0.50	mg/dL	0.2	1.2	.	Normal		
	Day 28	2020-01-10	Yes	0.49	mg/dL	0.2	1.2	.	Normal		
	Day 42	2020-01-22	Yes	0.55	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-02-05	Yes	0.43	mg/dL	0.2	1.2	.	Normal		
01-004	Screening	2019-11-15	Yes	0.43	mg/dl	0.2	1.3	.	Normal		
	Day 0	2019-12-13	Yes	0.36	mg/dL	0.2	1.2	.	Normal		
	Day 14	2019-12-27	Yes	0.49	mg/dL	0.2	1.2	.	Normal		
	Day 28	2020-01-09	Yes	0.32	mg/dL	0.2	1.2	.	Normal		
	Day 42	2020-01-23	Yes	0.41	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-02-10	Yes	0.38	mg/dL	0.2	1.2	.	Normal		
01-005	Screening	2019-11-15	Yes	0.46	mg/dl	0.2	1.3	.	Normal		
	Day 0	2019-12-13	Yes	0.35	mg/dL	0.2	1.2	.	Normal		
	Day 14	2019-12-27	Yes	0.44	mg/dL	0.2	1.2	.	Normal		
	Day 28	2020-01-10	Yes	0.25	mg/dL	0.2	1.2	.	Normal		
	Day 42	2020-01-24	Yes	0.27	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-02-07	Yes	0.24	mg/dL	0.2	1.2	.	Normal		
01-006	Screening	2019-11-20	Yes	0.61	mg/dl	0.2	1.3	.	Normal		

Listing 7.10 - Study IP-001-09 : Biochemistry - Total bilirubin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	0.50	mg/dL	0.2	1.2	.	Normal	
	Day 14	2020-01-03	Yes	0.71	mg/dL	0.2	1.2	.	Normal	
	Day 28	2020-01-15	Yes	0.35	mg/dL	0.2	1.2	.	Normal	
	Day 42	2020-01-29	Yes	0.53	mg/dL	0.2	1.2	.	Normal	
	Day 56	2020-02-12	Yes	0.50	mg/dL	0.2	1.2	.	Normal	
01-007	Screening	2019-11-21	No	0.54	mg/dl	0.2	1.3	.	Normal	
	Day 0	2019-12-19	Yes	0.37	mg/dL	0.2	1.2	.	Normal	
	Day 14	2020-01-03	Yes	0.37	mg/dL	0.2	1.2	.	Normal	
	Day 28	2020-01-16	Yes	0.30	mg/dL	0.2	1.2	.	Normal	
	Day 42	2020-01-30	Yes	0.36	mg/dL	0.2	1.2	.	Normal	
	Day 56	2020-02-13	Yes	0.36	mg/dL	0.2	1.2	.	Normal	
01-008	Screening	2019-11-21	Yes	0.96	mg/dl	0.2	1.3	.	Normal	
	Day 0	2019-12-19	Yes	0.77	mg/dL	0.2	1.2	.	Normal	
	Day 14	2020-01-03	Yes	0.75	mg/dL	0.2	1.2	.	Normal	
	Day 28	2020-01-16	Yes	0.70	mg/dL	0.2	1.2	.	Normal	
	Day 42	2020-01-30	Yes	0.65	mg/dL	0.2	1.2	.	Normal	
	Day 56	2020-02-13	Yes	0.64	mg/dL	0.2	1.2	.	Normal	
01-009	Screening	2019-11-26	Yes	0.62	mg/dl	0.2	1.3	.	Normal	
	Day 0	2019-12-23	Yes	0.61	mg/dL	0.2	1.2	.	Normal	
	Day 14	2020-01-07	Yes	0.66	mg/dL	0.2	1.2	.	Normal	
	Day 28	2020-01-21	Yes	0.53	mg/dL	0.2	1.2	.	Normal	
	Day 42	2020-02-04	Yes	0.55	mg/dL	0.2	1.2	.	Normal	
	Day 56	2020-02-18	Yes	0.49	mg/dL	0.2	1.2	.	Normal	
01-010	Screening	2019-12-12	Yes	0.33	mg/dL	0.2	1.2	.	Normal	
	Day 0	2020-01-08	Yes	0.43	mg/dL	0.2	1.2	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	0.47	mg/dL	0.2	1.2	.	Normal	
	Day 0	2020-03-05	Yes	0.55	mg/dL	0.2	1.2	.	Normal	

Listing 7.10 - Study IP-001-09 : Biochemistry - Total bilirubin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done		Evaluation	
01-011	Day 14	2020-03-20	Yes	0.52	mg/dL	0.2	1.2	.	Normal		
	Day 28	2020-04-02	Yes	0.57	mg/dL	0.2	1.2	.	Normal		
	Day 42	2020-04-16	Yes	0.57	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-04-30	Yes	0.44	mg/dL	0.2	1.2	.	Normal		
05-001	Screening	2021-10-13	No	0.32	mg/dL	0.2	1.0	.	Normal		
	Day 0	2021-11-10	Yes	0.30	mg/dL	0.2	1.0	.	Normal		
	Day 14	2021-11-26	Yes	0.30	mg/dL	0.2	1.0	.	Normal		
	Day 28	2021-12-09	Yes	0.20	mg/dL	0.2	1.0	.	Normal		
	Day 42	2022-01-28	Yes	0.25	mg/dL	0.2	1.0	.	Normal		
	Day 56	2022-02-22	Yes	.	mg/dL	0.2	1.0	Yes			.
05-002	Screening	2021-10-29	Yes	0.30	mg/dL	0.2	1.0	.	Normal		
	Day 0	2021-11-30	Yes	.	mg/dL	0.2	1.0	Yes			.
	Day 14	2021-12-14	Yes	0.30	mg/dL	0.2	1.0	.	Normal		
	Day 28	2021-12-30	Yes	0.31	mg/dL	0.2	1.0	.	Normal		
	Day 42	2022-01-15	Yes	0.34	mg/dL	0.2	1.0	.	Normal		
	Day 56	2022-02-03	Yes	0.30	mg/dL	0.2	1.0	.	Normal		
06-001	Screening	2021-12-15	Yes	.	mg/dl	0.3	1.2	Yes			.
06-002	Screening	2021-12-15	Yes	.	mg/dl	0.3	1.2	Yes			.

Listing 7.11 - Study IP-001-09 : Biochemistry - SGOT (AST)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	15	U/L	15	46	.	Normal
	Day 0	2019-11-13	Yes	20	U/L	15	46	.	Normal
	Day 14	2019-11-28	Yes	20	U/L	15	46	.	Normal
	Day 28	2019-12-12	Yes	14	U/L	5	34	.	Normal
	Day 42	2019-12-23	Yes	13	U/L	5	34	.	Normal
	Day 56	2020-01-07	Yes	11	U/L	5	34	.	Normal
01-002	Screening	2019-11-13	Yes	18	U/L	15	46	.	Normal
	Day 0	2019-12-11	Yes	15	U/L	5	34	.	Normal
	Day 14	2019-12-27	Yes	15	U/L	5	34	.	Normal
	Day 28	2020-01-08	Yes	12	U/L	5	34	.	Normal
	Day 42	2020-01-22	Yes	17	U/L	5	34	.	Normal
	Day 56	2020-02-05	Yes	12	U/L	5	34	.	Normal
01-003	Screening	2019-11-13	Yes	14	U/L	15	46	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	8	U/L	5	34	.	Normal
	Day 14	2019-12-27	Yes	9	U/L	5	34	.	Normal
	Day 28	2020-01-10	Yes	7	U/L	5	34	.	Normal
	Day 42	2020-01-22	Yes	9	U/L	5	34	.	Normal
	Day 56	2020-02-05	Yes	9	U/L	5	34	.	Normal
01-004	Screening	2019-11-15	Yes	21	U/L	14	36	.	Normal
	Day 0	2019-12-13	Yes	10	U/L	5	34	.	Normal
	Day 14	2019-12-27	Yes	11	U/L	5	34	.	Normal
	Day 28	2020-01-09	Yes	10	U/L	5	34	.	Normal
	Day 42	2020-01-23	Yes	10	U/L	5	34	.	Normal
	Day 56	2020-02-10	Yes	13	U/L	5	34	.	Normal
01-005	Screening	2019-11-15	Yes	17	U/L	15	46	.	Normal
	Day 0	2019-12-13	Yes	7	U/L	5	34	.	Normal
	Day 14	2019-12-27	Yes	11	U/L	5	34	.	Normal
	Day 28	2020-01-10	Yes	8	U/L	5	34	.	Normal
	Day 42	2020-01-24	Yes	9	U/L	5	34	.	Normal
	Day 56	2020-02-07	Yes	8	U/L	5	34	.	Normal
01-006	Screening	2019-11-20	Yes	22	U/L	15	46	.	Normal

Listing 7.11 - Study IP-001-09 : Biochemistry - SGOT (AST)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	10	U/L	5	34	.	Normal	
	Day 14	2020-01-03	Yes	19	U/L	5	34	.	Normal	
	Day 28	2020-01-15	Yes	22	U/L	5	34	.	Normal	
	Day 42	2020-01-29	Yes	16	U/L	5	34	.	Normal	
	Day 56	2020-02-12	Yes	13	U/L	5	34	.	Normal	
01-007	Screening	2019-11-21	No	18	U/L	15	46	.	Normal	
	Day 0	2019-12-19	Yes	15	U/L	5	34	.	Normal	
	Day 14	2020-01-03	Yes	13	U/L	5	34	.	Normal	
	Day 28	2020-01-16	Yes	10	U/L	5	34	.	Normal	
	Day 42	2020-01-30	Yes	10	U/L	5	34	.	Normal	
	Day 56	2020-02-13	Yes	7	U/L	5	34	.	Normal	
01-008	Screening	2019-11-21	Yes	32	U/L	15	46	.	Normal	
	Day 0	2019-12-19	Yes	18	U/L	5	34	.	Normal	
	Day 14	2020-01-03	Yes	18	U/L	5	34	.	Normal	
	Day 28	2020-01-16	Yes	21	U/L	5	34	.	Normal	
	Day 42	2020-01-30	Yes	18	U/L	5	34	.	Normal	
	Day 56	2020-02-13	Yes	13	U/L	5	34	.	Normal	
01-009	Screening	2019-11-26	Yes	19	U/L	14	36	.	Normal	
	Day 0	2019-12-23	Yes	14	U/L	5	34	.	Normal	
	Day 14	2020-01-07	Yes	14	U/L	5	34	.	Normal	
	Day 28	2020-01-21	Yes	15	U/L	5	34	.	Normal	
	Day 42	2020-02-04	Yes	16	U/L	5	34	.	Normal	
	Day 56	2020-02-18	Yes	16	U/L	5	34	.	Normal	
01-010	Screening	2019-12-12	Yes	16	U/L	5	34	.	Normal	
	Day 0	2020-01-08	Yes	17	U/L	5	34	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	13	U/L	5	34	.	Normal	
	Day 0	2020-03-05	Yes	15	U/L	5	34	.	Normal	

Listing 7.11 - Study IP-001-09 : Biochemistry - SGOT (AST)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-011	Day 14	2020-03-20	Yes	13	U/L	5	34	.	Normal	
	Day 28	2020-04-02	Yes	15	U/L	5	34	.	Normal	
	Day 42	2020-04-16	Yes	18	U/L	5	34	.	Normal	
	Day 56	2020-04-30	Yes	15	U/L	5	34	.	Normal	
05-001	Screening	2021-10-13	No	15	U/L	15	37	.	Normal	
	Day 0	2021-11-10	Yes	12	U/L	15	37	.	Not Clinically Significant	
	Day 14	2021-11-26	Yes	15	U/L	15	37	.	Normal	
	Day 28	2021-12-09	Yes	16	U/L	15	37	.	Normal	
	Day 42	2022-01-28	Yes	12	U/L	15	37	.	Not Clinically Significant	
	Day 56	2022-02-22	Yes	.	U/L	15	37	Yes		.
05-002	Screening	2021-10-29	Yes	14	U/L	15	37	.	Not Clinically Significant	
	Day 0	2021-11-30	Yes	.	U/L	15	37	Yes		.
	Day 14	2021-12-14	Yes	17	U/L	15	37	.	Normal	
	Day 28	2021-12-30	Yes	17	U/L	15	37	.	Normal	
	Day 42	2022-01-15	Yes	21	U/L	15	37	.	Normal	
	Day 56	2022-02-03	Yes	21	U/L	15	37	.	Normal	
06-001	Screening	2021-12-15	Yes	8	UI/L	7	45	.	Normal	
06-002	Screening	2021-12-15	Yes	13	UI/L	7	45	.	Not Clinically Significant	

Listing 7.12 - Study IP-001-09 : Biochemistry - SGPT (ALT)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	17	U/L	11	66	.	Normal
	Day 0	2019-11-13	Yes	16	U/L	11	66	.	Normal
	Day 14	2019-11-28	Yes	23	U/L	11	66	.	Normal
	Day 28	2019-12-12	Yes	15	U/L	0	55	.	Normal
	Day 42	2019-12-23	Yes	16	U/L	0	55	.	Normal
	Day 56	2020-01-07	Yes	16	U/L	0	55	.	Normal
01-002	Screening	2019-11-13	Yes	17	U/L	11	66	.	Normal
	Day 0	2019-12-11	Yes	16	U/L	0	55	.	Normal
	Day 14	2019-12-27	Yes	18	U/L	0	55	.	Normal
	Day 28	2020-01-08	Yes	13	U/L	0	55	.	Normal
	Day 42	2020-01-22	Yes	18	U/L	0	55	.	Normal
	Day 56	2020-02-05	Yes	14	U/L	0	55	.	Normal
01-003	Screening	2019-11-13	Yes	10	U/L	11	66	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	9	U/L	0	55	.	Normal
	Day 14	2019-12-27	Yes	9	U/L	0	55	.	Normal
	Day 28	2020-01-10	Yes	7	U/L	0	55	.	Normal
	Day 42	2020-01-22	Yes	9	U/L	0	55	.	Normal
	Day 56	2020-02-05	Yes	10	U/L	0	55	.	Normal
01-004	Screening	2019-11-15	Yes	18	U/L	9	52	.	Normal
	Day 0	2019-12-13	Yes	13	U/L	0	55	.	Normal
	Day 14	2019-12-27	Yes	13	U/L	0	55	.	Normal
	Day 28	2020-01-09	Yes	18	U/L	0	55	.	Normal
	Day 42	2020-01-23	Yes	14	U/L	0	55	.	Normal
	Day 56	2020-02-10	Yes	16	U/L	0	55	.	Normal
01-005	Screening	2019-11-15	Yes	16	U/L	11	66	.	Normal
	Day 0	2019-12-13	Yes	12	U/L	0	55	.	Normal
	Day 14	2019-12-27	Yes	18	U/L	0	55	.	Normal
	Day 28	2020-01-10	Yes	12	U/L	0	55	.	Normal
	Day 42	2020-01-24	Yes	14	U/L	0	55	.	Normal
	Day 56	2020-02-07	Yes	13	U/L	0	55	.	Normal
01-006	Screening	2019-11-20	Yes	21	U/L	11	66	.	Normal

Listing 7.12 - Study IP-001-09 : Biochemistry - SGPT (ALT)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	14	U/L	0	55	.	Normal	
	Day 14	2020-01-03	Yes	28	U/L	0	55	.	Normal	
	Day 28	2020-01-15	Yes	40	U/L	0	55	.	Normal	
	Day 42	2020-01-29	Yes	28	U/L	0	55	.	Normal	
	Day 56	2020-02-12	Yes	19	U/L	0	55	.	Normal	
01-007	Screening	2019-11-21	No	12	U/L	11	66	.	Normal	
	Day 0	2019-12-19	Yes	17	U/L	0	55	.	Normal	
	Day 14	2020-01-03	Yes	17	U/L	0	55	.	Normal	
	Day 28	2020-01-16	Yes	11	U/L	0	55	.	Normal	
	Day 42	2020-01-30	Yes	13	U/L	0	55	.	Normal	
	Day 56	2020-02-13	Yes	15	U/L	0	55	.	Normal	
01-008	Screening	2019-11-21	Yes	35	U/L	11	66	.	Normal	
	Day 0	2019-12-19	Yes	27	U/L	0	55	.	Normal	
	Day 14	2020-01-03	Yes	35	U/L	0	55	.	Normal	
	Day 28	2020-01-16	Yes	34	U/L	0	55	.	Normal	
	Day 42	2020-01-30	Yes	32	U/L	0	55	.	Normal	
	Day 56	2020-02-13	Yes	19	U/L	0	55	.	Normal	
01-009	Screening	2019-11-26	Yes	12	U/L	9	52	.	Normal	
	Day 0	2019-12-23	Yes	11	U/L	0	55	.	Normal	
	Day 14	2020-01-07	Yes	10	U/L	0	55	.	Normal	
	Day 28	2020-01-21	Yes	11	U/L	0	55	.	Normal	
	Day 42	2020-02-04	Yes	13	U/L	0	55	.	Normal	
	Day 56	2020-02-18	Yes	12	U/L	0	55	.	Normal	
01-010	Screening	2019-12-12	Yes	13	U/L	0	55	.	Normal	
	Day 0	2020-01-08	Yes	24	U/L	0	55	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	8	U/L	0	55	.	Normal	
	Day 0	2020-03-05	Yes	9	U/L	0	55	.	Normal	

Listing 7.12 - Study IP-001-09 : Biochemistry - SGPT (ALT)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-011	Day 14	2020-03-20	Yes	8	U/L	0	55	.	Normal	
	Day 28	2020-04-02	Yes	7	U/L	0	55	.	Normal	
	Day 42	2020-04-16	Yes	10	U/L	0	55	.	Normal	
	Day 56	2020-04-30	Yes	9	U/L	0	55	.	Normal	
05-001	Screening	2021-10-13	No	17	U/L	12	78	.	Normal	
	Day 0	2021-11-10	Yes	11	U/L	12	78	.	Not Clinically Significant	
	Day 14	2021-11-26	Yes	14	U/L	12	78	.	Normal	
	Day 28	2021-12-09	Yes	18	U/L	12	78	.	Normal	
	Day 42	2022-01-28	Yes	16	U/L	12	78	.	Normal	
	Day 56	2022-02-22	Yes	.	U/L	12	78	Yes		.
05-002	Screening	2021-10-29	Yes	18	U/L	12	78	.	Normal	
	Day 0	2021-11-30	Yes	.	U/L	12	78	Yes		.
	Day 14	2021-12-14	Yes	54	U/L	12	78	.	Normal	
	Day 28	2021-12-30	Yes	31	U/L	12	78	.	Normal	
	Day 42	2022-01-15	Yes	29	U/L	12	78	.	Normal	
	Day 56	2022-02-03	Yes	43	U/L	12	78	.	Normal	
06-001	Screening	2021-12-15	Yes	12	UI/L	7	45	.	Normal	
06-002	Screening	2021-12-15	Yes	20	UI/L	7	45	.	Not Clinically Significant	

Listing 7.13 - Study IP-001-09 : Biochemistry - Alkaline Phosphatase

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-001	Screening	2019-10-16	Yes	80	U/L	38	126	.	Normal	
	Day 0	2019-11-13	Yes	82	U/L	38	126	.	Normal	
	Day 14	2019-11-28	Yes	92	U/L	38	126	.	Normal	
	Day 28	2019-12-12	Yes	102	U/L	40	150	.	Normal	
	Day 42	2019-12-23	Yes	115	U/L	40	150	.	Normal	
	Day 56	2020-01-07	Yes	114	U/L	40	150	.	Normal	
01-002	Screening	2019-11-13	Yes	61	U/L	38	126	.	Normal	
	Day 0	2019-12-11	Yes	64	U/L	40	150	.	Normal	
	Day 14	2019-12-27	Yes	73	U/L	40	150	.	Normal	
	Day 28	2020-01-08	Yes	69	U/L	40	150	.	Normal	
	Day 42	2020-01-22	Yes	65	U/L	40	150	.	Normal	
	Day 56	2020-02-05	Yes	66	U/L	40	150	.	Normal	
01-003	Screening	2019-11-13	Yes	120	U/L	38	126	.	Normal	
	Day 0	2019-12-11	Yes	167	U/L	40	150	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	.	U/L	40	150	Yes		.
	Day 28	2020-01-10	Yes	185	U/L	40	150	.	Not Clinically Significant	
	Day 42	2020-01-22	Yes	164	U/L	40	150	.	Not Clinically Significant	
	Day 56	2020-02-05	Yes	196	U/L	40	150	.	Not Clinically Significant	
01-004	Screening	2019-11-15	Yes	50	U/L	38	126	.	Normal	
	Day 0	2019-12-13	Yes	67	U/L	40	150	.	Normal	
	Day 14	2019-12-27	Yes	63	U/L	40	150	.	Normal	
	Day 28	2020-01-09	Yes	64	U/L	40	150	.	Normal	
	Day 42	2020-01-23	Yes	59	U/L	40	150	.	Normal	
	Day 56	2020-02-10	Yes	63	U/L	40	150	.	Normal	
01-005	Screening	2019-11-15	Yes	52	U/L	38	126	.	Normal	
	Day 0	2019-12-13	Yes	56	U/L	40	150	.	Normal	
	Day 14	2019-12-27	Yes	.	U/L	40	150	Yes		.
	Day 28	2020-01-10	Yes	58	U/L	40	150	.	Normal	
	Day 42	2020-01-24	Yes	68	U/L	40	150	.	Normal	
	Day 56	2020-02-07	Yes	62	U/L	40	150	.	Normal	
01-006	Screening	2019-11-20	Yes	53	U/L	38	126	.	Normal	

Listing 7.13 - Study IP-001-09 : Biochemistry - Alkaline Phosphatase

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	53	U/L	40	150	.	Normal	
	Day 14	2020-01-03	Yes	54	U/L	40	150	.	Normal	
	Day 28	2020-01-15	Yes	.	U/L	40	150	Yes		.
	Day 42	2020-01-29	Yes	55	U/L	40	150	.	Normal	
	Day 56	2020-02-12	Yes	53	U/L	40	150	.	Normal	
01-007	Screening	2019-11-21	No	72	U/L	38	126	.	Normal	
	Day 0	2019-12-19	Yes	73	U/L	40	150	.	Normal	
	Day 14	2020-01-03	Yes	64	U/L	40	150	.	Normal	
	Day 28	2020-01-16	Yes	67	U/L	40	150	.	Normal	
	Day 42	2020-01-30	Yes	64	U/L	40	150	.	Normal	
	Day 56	2020-02-13	Yes	75	U/L	40	150	.	Normal	
01-008	Screening	2019-11-21	Yes	61	U/L	38	126	.	Normal	
	Day 0	2019-12-19	Yes	76	U/L	40	150	.	Normal	
	Day 14	2020-01-03	Yes	111	U/L	40	150	.	Normal	
	Day 28	2020-01-16	Yes	86	U/L	40	150	.	Normal	
	Day 42	2020-01-30	Yes	95	U/L	40	150	.	Normal	
	Day 56	2020-02-13	Yes	84	U/L	40	150	.	Normal	
01-009	Screening	2019-11-26	Yes	82	U/L	38	126	.	Normal	
	Day 0	2019-12-23	Yes	94	U/L	40	150	.	Normal	
	Day 14	2020-01-07	Yes	85	U/L	40	150	.	Normal	
	Day 28	2020-01-21	Yes	91	U/L	40	150	.	Normal	
	Day 42	2020-02-04	Yes	93	U/L	40	150	.	Normal	
	Day 56	2020-02-18	Yes	102	U/L	40	150	.	Normal	
01-010	Screening	2019-12-12	Yes	85	U/L	40	150	.	Normal	
	Day 0	2020-01-08	Yes	112	U/L	40	150	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	47	U/L	40	150	.	Normal	
	Day 0	2020-03-05	Yes	54	U/L	40	150	.	Normal	

Listing 7.13 - Study IP-001-09 : Biochemistry - Alkaline Phosphatase

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-011	Day 14	2020-03-20	Yes	38	U/L	40	150	.	Not Clinically Significant	
	Day 28	2020-04-02	Yes	43	U/L	40	150	.	Normal	
	Day 42	2020-04-16	Yes	38	U/L	40	150	.	Not Clinically Significant	
	Day 56	2020-04-30	Yes	44	U/L	40	150	.	Normal	
05-001	Screening	2021-10-13	No	163	U/L	43	115	.	Not Clinically Significant	
	Day 0	2021-11-10	Yes	114	U/L	43	115	.	Normal	
	Day 14	2021-11-26	Yes	161	U/L	43	115	.	Not Clinically Significant	
	Day 28	2021-12-09	Yes	147	U/L	43	115	.	Not Clinically Significant	
	Day 42	2022-01-28	Yes	153	U/L	43	115	.	Not Clinically Significant	
	Day 56	2022-02-22	Yes	.	U/L	43	115	Yes		.
05-002	Screening	2021-10-29	Yes	141	U/L	43	115	.	Not Clinically Significant	
	Day 0	2021-11-30	Yes	.	U/L	43	115	Yes		.
	Day 14	2021-12-14	Yes	115	U/L	43	115	.	Normal	
	Day 28	2021-12-30	Yes	132	U/L	43	115	.	Not Clinically Significant	
	Day 42	2022-01-15	Yes	171	U/L	43	115	.	Not Clinically Significant	
	Day 56	2022-02-03	Yes	159	U/L	43	115	.	Not Clinically Significant	
06-001	Screening	2021-12-15	Yes	151	UI/L	40	129	.	Not Clinically Significant	
06-002	Screening	2021-12-15	Yes	72	UI/L	40	129	.	Not Clinically Significant	

Listing 7.14 - Study IP-001-09 : Biochemistry - GGT

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	14	U/L	15	73	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	16	U/L	15	73	.	Normal
	Day 14	2019-11-28	Yes	23	U/L	15	73	.	Normal
	Day 28	2019-12-12	Yes	18	U/L	12	64	.	Normal
	Day 42	2019-12-23	Yes	16	U/L	12	64	.	Normal
	Day 56	2020-01-07	Yes	13	U/L	12	64	.	Normal
01-002	Screening	2019-11-13	Yes	15	U/L	15	73	.	Normal
	Day 0	2019-12-11	Yes	15	U/L	12	64	.	Normal
	Day 14	2019-12-27	Yes	15	U/L	12	64	.	Normal
	Day 28	2020-01-08	Yes	16	U/L	12	64	.	Normal
	Day 42	2020-01-22	Yes	17	U/L	12	64	.	Normal
	Day 56	2020-02-05	Yes	14	U/L	12	64	.	Normal
01-003	Screening	2019-11-13	Yes	13	U/L	15	73	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	14	U/L	12	64	.	Normal
	Day 14	2019-12-27	Yes	14	U/L	12	64	.	Normal
	Day 28	2020-01-10	Yes	185	U/L	12	64	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	12	U/L	12	64	.	Normal
	Day 56	2020-02-05	Yes	12	U/L	12	64	.	Normal
01-004	Screening	2019-11-15	Yes	10	U/L	12	43	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	10	U/L	9	36	.	Normal
	Day 14	2019-12-27	Yes	11	U/L	9	36	.	Normal
	Day 28	2020-01-09	Yes	14	U/L	9	36	.	Normal
	Day 42	2020-01-23	Yes	13	U/L	9	36	.	Normal
	Day 56	2020-02-10	Yes	12	U/L	9	36	.	Normal
01-005	Screening	2019-11-15	Yes	31	U/L	15	73	.	Normal
	Day 0	2019-12-13	Yes	33	U/L	12	64	.	Normal
	Day 14	2019-12-27	Yes	38	U/L	12	64	.	Normal
	Day 28	2020-01-10	Yes	43	U/L	12	64	.	Normal
	Day 42	2020-01-24	Yes	39	U/L	12	64	.	Normal
	Day 56	2020-02-07	Yes	34	U/L	12	64	.	Normal
01-006	Screening	2019-11-20	Yes	66	U/L	15	73	.	Normal

Listing 7.14 - Study IP-001-09 : Biochemistry - GGT

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	44	U/L	12	64	.	Normal	
	Day 14	2020-01-03	Yes	55	U/L	12	64	.	Normal	
	Day 28	2020-01-15	Yes	58	U/L	12	64	.	Normal	
	Day 42	2020-01-29	Yes	57	U/L	12	64	.	Normal	
	Day 56	2020-02-12	Yes	55	U/L	12	64	.	Normal	
01-007	Screening	2019-11-21	No	29	U/L	15	73	.	Normal	
	Day 0	2019-12-19	Yes	27	U/L	12	64	.	Normal	
	Day 14	2020-01-03	Yes	27	U/L	12	64	.	Normal	
	Day 28	2020-01-16	Yes	21	U/L	12	64	.	Normal	
	Day 42	2020-01-30	Yes	21	U/L	12	64	.	Normal	
	Day 56	2020-02-13	Yes	27	U/L	12	64	.	Normal	
01-008	Screening	2019-11-21	Yes	21	U/L	15	73	.	Normal	
	Day 0	2019-12-19	Yes	18	U/L	12	64	.	Normal	
	Day 14	2020-01-03	Yes	26	U/L	12	64	.	Normal	
	Day 28	2020-01-16	Yes	28	U/L	12	64	.	Normal	
	Day 42	2020-01-30	Yes	24	U/L	12	64	.	Normal	
	Day 56	2020-02-13	Yes	23	U/L	12	64	.	Normal	
01-009	Screening	2019-11-26	Yes	19	U/L	12	43	.	Normal	
	Day 0	2019-12-23	Yes	16	U/L	9	36	.	Normal	
	Day 14	2020-01-07	Yes	18	U/L	9	36	.	Normal	
	Day 28	2020-01-21	Yes	17	U/L	9	36	.	Normal	
	Day 42	2020-02-04	Yes	17	U/L	9	36	.	Normal	
	Day 56	2020-02-18	Yes	18	U/L	9	36	.	Normal	
01-010	Screening	2019-12-12	Yes	19	U/L	12	64	.	Normal	
	Day 0	2020-01-08	Yes	25	U/L	12	64	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	10	U/L	9	36	.	Normal	
	Day 0	2020-03-05	Yes	11	U/L	9	36	.	Normal	

Listing 7.14 - Study IP-001-09 : Biochemistry - GGT

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-011	Day 14	2020-03-20	Yes	10	U/L	9	36	.	Normal	
	Day 28	2020-04-02	Yes	11	U/L	9	36	.	Normal	
	Day 42	2020-04-16	Yes	69	U/L	9	36	.	Not Clinically Significant	
	Day 56	2020-04-30	Yes	13	U/L	9	36	.	Normal	
05-001	Screening	2021-10-13	No	14	U/L	15	85	.	Not Clinically Significant	
	Day 0	2021-11-10	Yes	12	U/L	15	85	.	Not Clinically Significant	
	Day 14	2021-11-26	Yes	19	U/L	15	85	.	Normal	
	Day 28	2021-12-09	Yes	17	U/L	15	85	.	Normal	
	Day 42	2022-01-28	Yes	13	U/L	15	85	.	Not Clinically Significant	
	Day 56	2022-02-22	Yes	.	U/L	15	85	Yes		.
05-002	Screening	2021-10-29	Yes	74	U/L	15	85	.	Normal	
	Day 0	2021-11-30	Yes	.	U/L	15	85	Yes		.
	Day 14	2021-12-14	Yes	55	U/L	15	85	.	Normal	
	Day 28	2021-12-30	Yes	66	U/L	15	85	.	Normal	
	Day 42	2022-01-15	Yes	96	U/L	15	85	.	Not Clinically Significant	
	Day 56	2022-02-03	Yes	80	U/L	15	85	.	Normal	
06-001	Screening	2021-12-15	Yes	15	UI/L	8	61	.	Normal	
06-002	Screening	2021-12-15	Yes	8	UI/L	8	61	.	Not Clinically Significant	

Listing 7.15 - Study IP-001-09 : Biochemistry - Serum Sodium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	137.0	mmol/L	136	146	.	Normal
	Day 0	2019-11-13	Yes	143.0	mmol/L	136	146	.	Normal
	Day 14	2019-11-28	Yes	140.0	mmol/L	136	146	.	Normal
	Day 28	2019-12-12	Yes	140.0	mmol/L	136	146	.	Normal
	Day 42	2019-12-23	Yes	140.0	mmol/L	136	146	.	Normal
	Day 56	2020-01-07	Yes	141.0	mmol/L	136	146	.	Normal
01-002	Screening	2019-11-13	Yes	137.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-11	Yes	138.0	mmol/L	136	146	.	Normal
	Day 14	2019-12-27	Yes	136.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-08	Yes	136.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-22	Yes	137.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-05	Yes	135.0	mmol/L	136	146	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	138.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-11	Yes	140.0	mmol/L	136	146	.	Normal
	Day 14	2019-12-27	Yes	137.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-10	Yes	137.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-22	Yes	137.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-05	Yes	140.0	mmol/L	136	146	.	Normal
01-004	Screening	2019-11-15	Yes	136.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-13	Yes	138.0	mmol/L	136	146	.	Normal
	Day 14	2019-12-27	Yes	136.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-09	Yes	135.0	mmol/L	136	146	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	137.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-10	Yes	137.0	mmol/L	136	146	.	Normal
01-005	Screening	2019-11-15	Yes	137.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-13	Yes	136.0	mmol/L	136	146	.	Normal
	Day 14	2019-12-27	Yes	139.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-10	Yes	136.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-24	Yes	134.0	mmol/L	136	146	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	136.0	mmol/L	136	146	.	Normal
01-006	Screening	2019-11-20	Yes	143.0	mmol/L	136	146	.	Normal

Listing 7.15 - Study IP-001-09 : Biochemistry - Serum Sodium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	141.0	mmol/L	136	146	.	Normal
	Day 14	2020-01-03	Yes	145.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-15	Yes	143.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-29	Yes	145.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-12	Yes	141.0	mmol/L	136	146	.	Normal
01-007	Screening	2019-11-21	No	136.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-19	Yes	138.0	mmol/L	136	146	.	Normal
	Day 14	2020-01-03	Yes	138.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-16	Yes	139.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-30	Yes	135.0	mmol/L	136	146	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	136.0	mmol/L	136	146	.	Normal
01-008	Screening	2019-11-21	Yes	142.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-19	Yes	141.0	mmol/L	136	146	.	Normal
	Day 14	2020-01-03	Yes	141.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-16	Yes	142.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-30	Yes	139.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-13	Yes	138.0	mmol/L	136	146	.	Normal
01-009	Screening	2019-11-26	Yes	140.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-23	Yes	135.0	mmol/L	136	146	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	138.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-21	Yes	135.0	mmol/L	136	146	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	137.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-18	Yes	136.0	mmol/L	136	146	.	Normal
01-010	Screening	2019-12-12	Yes	140.0	mmol/L	136	146	.	Normal
	Day 0	2020-01-08	Yes	140.0	mmol/L	136	146	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	142.0	mmol/L	136	146	.	Normal
	Day 0	2020-03-05	Yes	138.0	mmol/L	136	146	.	Normal

Listing 7.15 - Study IP-001-09 : Biochemistry - Serum Sodium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	140.0	mmol/L	136	146	.	Normal
	Day 28	2020-04-02	Yes	140.0	mmol/L	136	146	.	Normal
	Day 42	2020-04-16	Yes	144.0	mmol/L	136	146	.	Normal
	Day 56	2020-04-30	Yes	3.8	mmol/L	136	146	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	139.0	mEq/L	136	145	.	Normal
	Day 0	2021-11-10	Yes	130.0	mEq/L	136	145	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	135.0	mEq/L	136	145	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	139.0	mEq/L	136	145	.	Normal
	Day 42	2022-01-28	Yes	133.0	mEq/L	136	145	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	133.0	mEq/L	136	145	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	132.0	mEq/L	136	145	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	131.0	mEq/L	136	145	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	133.0	mEq/L	136	145	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	133.0	mEq/L	136	145	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	132.0	mEq/L	136	145	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	131.0	mEq/L	136	145	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	137.0	mmol/L	135	145	.	Normal
06-002	Screening	2021-12-15	Yes	143.0	mmol/L	135	145	.	Not Clinically Significant

Listing 7.16 - Study IP-001-09 : Biochemistry - Potassium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	5.45	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	5.37	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	5.55	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	5.50	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	5.50	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	5.30	mmol/L	3.5	5.1	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	5.37	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	4.40	mmol/L	3.5	5.1	.	Normal
	Day 14	2019-12-27	Yes	4.70	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-01-08	Yes	4.50	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-22	Yes	5.20	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	4.10	mmol/L	3.5	5.1	.	Normal
01-003	Screening	2019-11-13	Yes	4.18	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-11	Yes	4.20	mmol/L	3.5	5.1	.	Normal
	Day 14	2019-12-27	Yes	3.90	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-01-10	Yes	3.80	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-22	Yes	4.30	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-02-05	Yes	4.60	mmol/L	3.5	5.1	.	Normal
01-004	Screening	2019-11-15	Yes	5.03	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-13	Yes	4.90	mmol/L	3.5	5.1	.	Normal
	Day 14	2019-12-27	Yes	5.10	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-01-09	Yes	5.00	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-23	Yes	5.20	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	5.00	mmol/L	3.5	5.1	.	Normal
01-005	Screening	2019-11-15	Yes	4.99	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-13	Yes	4.50	mmol/L	3.5	5.1	.	Normal
	Day 14	2019-12-27	Yes	4.30	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-01-10	Yes	4.30	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-24	Yes	4.50	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-02-07	Yes	4.60	mmol/L	3.5	5.1	.	Normal
01-006	Screening	2019-11-20	Yes	3.52	mmol/L	3.5	5.1	.	Normal

Listing 7.16 - Study IP-001-09 : Biochemistry - Potassium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	3.40	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	3.30	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	3.30	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	3.50	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-02-12	Yes	3.50	mmol/L	3.5	5.1	.	Normal
01-007	Screening	2019-11-21	No	4.77	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-19	Yes	4.60	mmol/L	3.5	5.1	.	Normal
	Day 14	2020-01-03	Yes	5.30	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	4.60	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-30	Yes	5.30	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	5.20	mmol/L	3.5	5.1	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	4.72	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-19	Yes	5.00	mmol/L	3.5	5.1	.	Normal
	Day 14	2020-01-03	Yes	4.60	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-01-16	Yes	4.80	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-30	Yes	4.80	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-02-13	Yes	4.30	mmol/L	3.5	5.1	.	Normal
01-009	Screening	2019-11-26	Yes	4.73	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-23	Yes	5.20	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	5.30	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	4.70	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-02-04	Yes	4.90	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-02-18	Yes	4.60	mmol/L	3.5	5.1	.	Normal
01-010	Screening	2019-12-12	Yes	4.70	mmol/L	3.5	5.1	.	Normal
	Day 0	2020-01-08	Yes	4.50	mmol/L	3.5	5.1	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	4.90	mmol/L	3.5	5.1	.	Normal
	Day 0	2020-03-05	Yes	4.90	mmol/L	3.5	5.1	.	Normal

Listing 7.16 - Study IP-001-09 : Biochemistry - Potassium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	4.60	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-04-02	Yes	4.30	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-04-16	Yes	4.50	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-04-30	Yes	3.70	mmol/L	3.5	5.1	.	Normal
05-001	Screening	2021-10-13	No	4.50	mEq/L	3.5	5.0	.	Normal
	Day 0	2021-11-10	Yes	3.50	mEq/L	3.5	5.0	.	Normal
	Day 14	2021-11-26	Yes	5.60	mEq/L	3.5	5.0	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	4.50	mEq/L	3.5	5.0	.	Normal
	Day 42	2022-01-28	Yes	4.50	mEq/L	3.5	5.0	.	Normal
	Day 56	2022-02-22	Yes	4.60	mEq/L	3.5	5.0	.	Normal
05-002	Screening	2021-10-29	Yes	4.00	mEq/L	3.5	5.0	.	Normal
	Day 0	2021-11-30	Yes	4.90	mEq/L	3.5	5.0	.	Normal
	Day 14	2021-12-14	Yes	3.90	mEq/L	3.5	5.0	.	Normal
	Day 28	2021-12-30	Yes	3.90	mEq/L	3.5	5.0	.	Normal
	Day 42	2022-01-15	Yes	3.80	mEq/L	3.5	5.0	.	Normal
	Day 56	2022-02-03	Yes	3.80	mEq/L	3.5	5.0	.	Normal
06-001	Screening	2021-12-15	Yes	3.90	mmol/L	3.5	5.0	.	Normal
06-002	Screening	2021-12-15	Yes	4.40	mmol/L	3.5	5.0	.	Not Clinically Significant

Listing 7.17 - Study IP-001-09 : Biochemistry - Calcium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	2.4	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-11-13	Yes	2.4	mmol/L	2.1	2.55	.	Normal
	Day 14	2019-11-28	Yes	2.4	mmol/L	2.1	2.55	.	Normal
	Day 28	2019-12-12	Yes	8.9	mg/dL	8.8	10.20	.	Normal
	Day 42	2019-12-23	Yes	9.4	mg/dL	8.8	10.20	.	Normal
	Day 56	2020-01-07	Yes	9.2	mg/dL	8.8	10.20	.	Normal
01-002	Screening	2019-11-13	Yes	2.2	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-11	Yes	8.9	mg/dL	8.8	10.20	.	Normal
	Day 14	2019-12-27	Yes	8.4	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	9.3	mg/dL	8.8	10.20	.	Normal
	Day 42	2020-01-22	Yes	8.5	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	8.7	mg/dL	8.8	10.20	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	2.2	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-11	Yes	8.8	mg/dL	8.8	10.20	.	Normal
	Day 14	2019-12-27	Yes	8.3	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	8.5	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	8.5	mg/dL	8.8	10.20	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	2.3	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-13	Yes	8.9	mg/dL	8.8	10.20	.	Normal
	Day 14	2019-12-27	Yes	9.0	mg/dL	8.8	10.20	.	Normal
	Day 28	2020-01-09	Yes	9.2	mg/dL	8.8	10.20	.	Normal
	Day 42	2020-01-23	Yes	9.0	mg/dL	8.8	10.20	.	Normal
	Day 56	2020-02-10	Yes	8.9	mg/dL	8.8	10.20	.	Normal
01-005	Screening	2019-11-15	Yes	2.2	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-13	Yes	9.1	mg/dL	8.8	10.20	.	Normal
	Day 14	2019-12-27	Yes	9.5	mg/dL	8.8	10.20	.	Normal
	Day 28	2020-01-10	Yes	9.6	mg/dL	8.8	10.20	.	Normal
	Day 42	2020-01-24	Yes	9.6	mg/dL	8.8	10.20	.	Normal
	Day 56	2020-02-07	Yes	9.0	mg/dL	8.8	10.20	.	Normal
01-006	Screening	2019-11-20	Yes	2.2	mmol/L	2.1	2.55	.	Normal

Listing 7.17 - Study IP-001-09 : Biochemistry - Calcium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	8.4	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	8.4	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	8.5	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	8.8	mg/dL	8.8	10.20	.	Normal
01-007	Screening	2019-11-21	No	2.4	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-19	Yes	11.9	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	8.7	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	8.0	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	8.4	mg/dL	8.8	10.20	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	2.5	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-19	Yes	10.0	mg/dL	8.8	10.20	.	Normal
	Day 14	2020-01-03	Yes	9.4	mg/dL	8.8	10.20	.	Normal
	Day 28	2020-01-16	Yes	10.5	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	10.5	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	2.3	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-23	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	9.2	mg/dL	8.8	10.20	.	Normal
	Day 28	2020-01-21	Yes	8.4	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	8.7	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	8.5	mg/dL	8.8	10.20	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	7.6	mg/dL	8.8	10.20	.	Clinically sign. for the pathology under study
	Day 0	2020-01-08	Yes	7.9	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	9.2	mg/dL	8.8	10.20	.	Normal
	Day 0	2020-03-05	Yes	9.8	mg/dL	8.8	10.20	.	Normal

Listing 7.17 - Study IP-001-09 : Biochemistry - Calcium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	9.5	mg/dL	8.8	10.20	.	Normal
	Day 28	2020-04-02	Yes	9.7	mg/dL	8.8	10.20	.	Normal
	Day 42	2020-04-16	Yes	10.1	mg/dL	8.8	10.20	.	Normal
	Day 56	2020-04-30	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	7.7	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	7.3	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	8.3	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	7.8	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	8.0	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	9.0	mg/dL	8.5	10.10	.	Normal
05-002	Screening	2021-10-29	Yes	8.5	mg/dL	8.5	10.10	.	Normal
	Day 0	2021-11-30	Yes	8.2	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	8.3	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	8.6	mg/dL	8.5	10.10	.	Normal
	Day 42	2022-01-15	Yes	8.7	mg/dL	8.5	10.10	.	Normal
	Day 56	2022-02-03	Yes	8.3	mg/dL	8.5	10.10	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	8.7	mg/dL	8.6	10.20	.	Normal
06-002	Screening	2021-12-15	Yes	9.9	mg/dL	8.6	10.20	.	Not Clinically Significant

Listing 7.18 - Study IP-001-09 : Biochemistry - Phosphorus

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	1.90	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	1.70	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	1.80	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	5.80	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	5.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	5.70	mg/dL	2.30	4.30	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	1.60	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	4.60	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	5.70	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	4.50	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	4.90	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	4.60	mg/dL	2.30	4.30	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	0.81	mmol/L	0.81	1.45	.	Clinically significant for concomitant disease
	Day 0	2019-12-11	Yes	6.60	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	6.70	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	6.60	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	6.40	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	6.50	mg/dL	2.30	4.30	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	2.20	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	5.70	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	7.10	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	5.70	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	6.40	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	6.50	mg/dL	2.30	4.30	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	1.80	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	6.20	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	5.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	5.10	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	5.50	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	5.40	mg/dL	2.30	4.30	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	1.40	mmol/L	0.81	1.45	.	Normal

Listing 7.18 - Study IP-001-09 : Biochemistry - Phosphorus

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	4.10	mg/dL	2.30	4.30	.	Normal
	Day 14	2020-01-03	Yes	4.50	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	3.40	mg/dL	2.30	4.30	.	Normal
	Day 42	2020-01-29	Yes	4.00	mg/dL	2.30	4.30	.	Normal
	Day 56	2020-02-12	Yes	4.50	mg/dL	2.30	4.30	.	Not Clinically Significant
01-007	Screening	2019-11-21	No	2.10	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	6.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	7.00	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	7.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	6.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	6.40	mg/dL	2.30	4.30	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	1.80	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	4.60	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	3.20	mg/dL	2.30	4.30	.	Normal
	Day 28	2020-01-16	Yes	5.40	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	3.80	mg/dL	2.30	4.30	.	Normal
	Day 56	2020-02-13	Yes	5.40	mg/dL	2.30	4.30	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	1.60	mmol/L	0.81	1.45	.	Clinically sign. for the pathology under study
	Day 0	2019-12-23	Yes	4.60	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	4.90	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	4.90	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	4.80	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	4.50	mg/dL	2.30	4.30	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	5.40	mg/dL	2.30	4.30	.	Clinically sign. for the pathology under study
	Day 0	2020-01-08	Yes	5.70	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	5.40	mg/dL	2.30	4.30	.	Clinically sign. for the pathology under study
	Day 0	2020-03-05	Yes	5.20	mg/dL	2.30	4.30	.	Not Clinically Significant

Listing 7.18 - Study IP-001-09 : Biochemistry - Phosphorus

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	4.80	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	4.90	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	6.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	5.10	mg/dL	2.30	4.30	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	4.00	mg/dL	2.50	4.90	.	Normal
	Day 0	2021-11-10	Yes	4.40	mg/dL	2.50	4.90	.	Normal
	Day 14	2021-11-26	Yes	3.90	mg/dL	2.50	4.90	.	Normal
	Day 28	2021-12-09	Yes	3.70	mg/dL	2.50	4.90	.	Normal
	Day 42	2022-01-28	Yes	5.60	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	6.30	mg/dL	2.50	4.90	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	7.00	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	6.00	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	5.40	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	6.30	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	6.10	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	5.80	mg/dL	2.50	4.90	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	4.80	mg/dL	2.50	4.50	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	4.30	mg/dL	2.50	4.50	.	Not Clinically Significant

Listing 8 - Study IP-001-09 : Weekly Total Urea Kt/v, Peritoneal Equilibration Test (PET) and Weekly total Creatinine Clearance

Patient no.	Visit no.	Weekly Total urea Kt/v	PET Dialysate/ Plasma creatinine	Weekly Total Creatinine Clearance
01-001	Day 0	0.76	0.66	61.46
	Day 28	1.52	0.74	69.88
	Day 56	1.58	0.70	70.98
01-002	Day 0	1.59	0.59	86.94
	Day 28	1.75	0.64	98.15
	Day 56	1.56	0.68	80.70
01-003	Day 0	1.45	0.61	72.22
	Day 28	1.54	0.67	65.83
	Day 56	1.35	0.70	68.22
01-004	Day 0	1.24	0.61	50.03
	Day 28	1.08	0.66	42.38
	Day 56	1.14	0.51	42.60
01-005	Day 0	1.10	0.22	78.04
	Day 28	1.07	0.72	55.45
	Day 56	1.06	0.70	59.66
01-006	Day 0	1.68	0.62	93.39
	Day 28	1.70	0.63	105.74
	Day 56	1.49	0.57	91.53
01-007	Day 0	1.52	0.57	77.76
	Day 28	1.57	0.60	79.55
	Day 56	1.14	0.62	58.06
01-008	Day 0	1.36	0.53	62.62
	Day 28	1.47	0.56	65.56
	Day 56	1.35	0.53	62.31
01-009	Day 0	1.43	0.57	85.52

Listing 8 - Study IP-001-09 : Weekly Total Urea Kt/v, Peritoneal Equilibration Test (PET) and Weekly total Creatinine Clearance

Patient no.	Visit no.	Weekly Total urea Kt/v	PET Dialysate/ Plasma creatinine	Weekly Total Creatinine Clearance
01-009	Day 28	1.42	0.59	95.78
	Day 56	1.84	0.57	112.38
01-010	Day 0	0.95	0.63	50.70
	Day 28	.	.	.
	Day 56	.	.	.
01-011	Day 0	1.12	0.48	55.46
	Day 28	1.42	0.61	80.25
	Day 56	1.49	0.53	65.26
05-001	Day 0	1.20	0.71	53.87
	Day 28	1.29	0.71	51.85
	Day 56	.	.	.
05-002	Day 0	1.23	0.71	43.28
	Day 28	1.12	0.59	42.69
	Day 56	1.12	0.62	42.83

Listing 9 - Study IP-001-09 : Subjective questionnaire

Patient no.	Visit no.	Questionnaire filled	Questionnaire Total score
01-001	Day 0	Yes	15
	Day 28	Yes	15
	Day 56	Yes	15
01-002	Day 0	Yes	15
	Day 28	Yes	15
	Day 56	Yes	15
01-003	Day 0	Yes	17
	Day 28	Yes	20
	Day 56	Yes	23
01-004	Day 0	Yes	14
	Day 28	Yes	19
	Day 56	Yes	16
01-005	Day 0	Yes	25
	Day 28	Yes	18
	Day 56	Yes	18
01-006	Day 0	Yes	22
	Day 28	Yes	18
	Day 56	Yes	15
01-007	Day 0	Yes	17
	Day 28	Yes	21
	Day 56	Yes	19
01-008	Day 0	Yes	17
	Day 28	Yes	16
	Day 56	Yes	15
01-009	Day 0	Yes	16
	Day 28	Yes	17
	Day 56	Yes	15

Listing 9 - Study IP-001-09 : Subjective questionnaire

Patient no.	Visit no.	Questionnaire filled	Questionnaire Total score
01-010	Day 0	Yes	17
	Day 28		.
	Day 56		.
01-011	Day 0	Yes	19
	Day 28	Yes	17
	Day 56	Yes	16
05-001	Day 0	Yes	20
	Day 28	Yes	26
	Day 56	No	.
05-002	Day 0	Yes	21
	Day 28	Yes	25
	Day 56	Yes	24

Listing 10 - Study IP-001-09 : ECG - evaluation

Patient no.	Visit no.	ECG normal	ECG abnormality	ECG evaluation
01-001	Day 0	No	Sinus Bradycardia	Clinically significant for concomitant disease
	Day 28	No	Sinus Bradycardia	Clinically sign. for the pathology under study
01-002	Day 0	Yes	.	.
	Day 28	Yes	.	.
01-003	Day 0	Yes	.	.
	Day 28	Yes	.	.
01-004	Day 0	Yes	.	.
	Day 28	Yes	.	.
01-005	Day 0	No	Sinus Bradycardia	Clinically significant for concomitant disease
	Day 28	Yes	.	.
01-006	Day 0	No	Sinus Bradycardia	Clinically significant for concomitant disease
	Day 28	No	Right Bundle Branch Block	Clinically significant for concomitant disease
01-007	Day 0	No	Left Bundle Branch Block	Clinically significant for concomitant disease
	Day 28	No	Left Bundle Branch Block	Clinically significant for concomitant disease
01-008	Day 0	Yes	.	.
	Day 28	Yes	.	.
01-009	Day 0	No	Other: Sinus rhythm, previous lower myocardial infarction	Clinically significant for concomitant disease
	Day 28	Yes	.	.
01-010	Day 0	Yes	.	.
01-011	Day 0	Yes	.	.
	Day 28	Yes	.	.

Listing 10 - Study IP-001-09 : ECG - evaluation

Patient no.	Visit no.	ECG normal	ECG abnormality	ECG evaluation
05-001	Day 0	Yes	.	.
	Day 28	Yes	.	.
05-002	Day 0	Yes	.	.
	Day 28	Yes	.	.

Listing 11 - Study IP-001-09 : Adverse events (AE)

Patient no.	AE num.	Event	Start date (yy-mm-dd)	End date (yy-mm-dd)	Seriousness	Intensity	Relation to study drug	Action taken	Outcome
01-002	1	Turbid peritoneal fluid	2019-12-27		Not serious	Mild	Not related	None	Not recovered
01-003	1	Anemia	2019-12-11		Not serious	Mild	Not related	Specific therapy/medication	Not recovered
01-004	1	Hyperphosphataemia	2019-12-27		Not serious	Mild	Not related	None	Not recovered
05-001	1	Macroglossia	2021-12-09		Not serious	Mild	Unlikely related	None	Not recovered
	2	insomnia	2021-12-05		Not serious	Mild	Not related	None	Not recovered
	3	Dispnea	2021-12-18		Not serious	Mild	Unlikely related	Specific therapy/medication	Not recovered
05-002	1	itching	2021-11-04		Not serious	Mild	Not related	None	Not recovered
	2	swollen legs	2021-12-19		Not serious	Mild	Unlikely related	None	Not recovered
	3	mild bilateral legs edema	2022-02-03		Not serious	Mild	Unlikely related	None	Not recovered

Listing 12 - Study IP-001-09 : Previous and Concomitant medications (CM)

Patient no.	Medication	Start date (dd/mm/yy)	End date (dd/mm/yy)	Ongoing	Total dose	Unit	Frequency	Route	Indication
01-001	Atenololo	13/12/2019		Yes	50.00	mg	QD	PO	Hypertension
	lasix	na/na/2015		Yes	50.00	mg	BID	PO	hypertension
	goltor	na/na/2017		Yes	.	mg	QD	PO	hypercholesterolemia
	rocaltrol	na/na/2019		Yes	.	mcg	QD	PO	CKD-MBD
	coral	na/na/2017		Yes	30.00	mg	QD	PO	hypertension
	esomeprazolo	na/na/2015		Yes	20.00	mg	QD	PO	GERD
	Atenololo	na/na/2015	12/12/2019	No	100.00	mg	QD	PO	hypertension
	zyloric	na/na/2017		Yes	300.00	mg	QD	PO	hyperuricemia
	renagel	na/04/2019		Yes	3200.00	mg	BID	PO	CKD-MBD
	olpress	na/na/2015		Yes	20.00	mg	QD	PO	hypertension
01-002	Zyloric	na/na/2018		Yes	300.00	mg	ONCE	PO	Hyperuricemia
	rocaltrol	na/05/2019		Yes	.	mcg	ONCE	PO	CKD-MBD
	diuresix	na/na/2010		Yes	10.00	mg	ONCE	PO	hypertension
	vytorin	na/na/2015		Yes	.	mg	ONCE	PO	hypercholesterolemia
	cardura	na/na/2010		Yes	4.00	mg	ONCE	PO	hypertension
	Tenormin	na/na/2007		Yes	25.00	mg	ONCE	PO	Post infarct heart disease
	cacit	na/05/2019		Yes	2000.00	mg	BID	PO	CKD-MBD
	lantus	na/na/2013		Yes	12.00	UI	ONCE	SC	diabetes mellitus
	apidra	na/na/2013		Yes	30.00	UI	TID	SC	diabetes mellitus
	plavix	na/na/2015		Yes	75.00	mg	ONCE	PO	secondary prevention
01-003	zyloric	na/na/2018		Yes	300.00	mg	ONCE	PO	hyperuricemia
	xatral	na/na/2005		Yes	10.00	mg	ONCE	PO	Benign prostatic hypertrophy
	mimpara	na/08/2019		Yes	30.00	mg	ONCE	PO	CKD-MBD
	renagel	na/06/2019		Yes	7200.00	mg	TID	PO	CKD-MBD
	binocrit	20/12/2019		Yes	6000.00	UI	OTH	SC	secondary anemia
01-004	lasix	na/na/2014		Yes	50.00	mg	BID	PO	hypertension
	dilatrend	na/na/2014		Yes	.	mg	BID	PO	hypertension
	binocrit	na/09/2019		Yes	6000.00	UI	OTH	SC	secondary anemia
	adalat crono	na/na/2019		Yes	30.00	mg	ONCE	PO	hypertension
	renagel	na/06/2019	27/12/2019	No	1600.00	mg	ONCE	PO	CKD-MBD
	maalox	27/12/2019		Yes	1.00	spoon	BID	PO	hyperphosphataemia
	rocaltrol	na/06/2019		Yes	.	mcg	ONCE	PO	CKD-MBD
	goltor	na/na/2017		Yes	.	mg	ONCE	PO	hypercholesterolemia
	zyloric	na/06/2019		Yes	150.00	mg	ONCE	PO	hyperuricemia
	omeprazolo	na/na/2015		Yes	10.00	mg	ONCE	PO	GERD
01-005	repaglinide	na/na/2010		Yes	2.00	mg	BID	PO	diebetes mellitus
	cardura	na/na/2010		Yes	4.00	mg	ONCE	PO	hypertension

Listing 12 - Study IP-001-09 : Previous and Concomitant medications (CM)

Patient no.	Medication	Start date (dd/mm/yy)	End date (dd/mm/yy)	Ongoing	Total dose	Unit	Frequency	Route	Indication
01-005	adalat crono	na/na/2010		Yes	120.00	mg	BID	PO	hypertension
	rocaltrol	na/06/2019		Yes	0.25	mcg	ONCE	PO	CKD-MBD
	eskim	na/na/2003		Yes	2000.00	mg	BID	PO	dyslipidemia
	retacrit	na/08/2019		Yes	4000.00	UI	OTH	SC	secondary anemia
	lasix	na/na/2018		Yes	250.00	mg	BID	PO	hypertension
	congescor	na/na/2010		Yes	2.50	mg	ONCE	PO	hypertension
	zyloric	na/na/2017		Yes	150.00	mg	ONCE	PO	hyperuricemia
	cacit	na/06/2019		Yes	2000.00	mg	BID	PO	CKD-MBD
01-006	Nebivololo	na/na/2018		Yes	.	mg	QD	PO	Hypertension
	Binocrit	na/na/2019		Yes	4000.00	UI	OTH	SC	Secondary anemia
	Lansoprazolo	na/na/2015		Yes	15.00	mg	QD	PO	Gastroprotective
	Cardioaspirina	na/na/2010		Yes	100.00	mg	QD	PO	Antiplatelet
	Rocaltrol	na/na/2018		Yes	.	mcg	QD	PO	CKB-MBD
	Lasix	na/na/2018		Yes	250.00	mg	QD	PO	Hypertension
	Cardura	na/na/2015		Yes	8.00	mg	QD	PO	Hypertension
	Adenuric	na/na/2019		Yes	160.00	mg	OTH	PO	Hyperuricemia
	Eutirox	na/na/2005		Yes	100.00	mcg	QD	PO	Hypothyroidism
01-007	Cardioaspirina	na/na/2015		Yes	100.00	mg	QD	PO	Heart attack prevention
	Amlodipina	na/na/2015		Yes	10.00	mg	QD	PO	Hypertension
	Adenuric	na/na/2015		Yes	80.00	mg	QD	PO	Hyperuricemia
	Alprazolam	na/na/2010		Yes	1.00	mg	QD	PO	Anxious syndrome
	Renagel	20/12/2019		Yes	3200.00	mg	QD	PO	CKD-MBD
	Lasix	na/na/2015		Yes	25.00	mg	QD	PO	Hypertension
	Rocaltrol	na/na/2017		Yes	.	mcg	QD	PO	CKD-MBD
	Sequacor	na/na/2015		Yes	.	mg	QD	PO	Prevention heart attack
	Omega 3	na/na/2015		Yes	3000.00	mg	QD	PO	Dyslipidemia
	Atorvastatina	na/na/2015		Yes	20.00	mg	QD	PO	Dyslipidemia
	Binocrit	na/na/2015		Yes	6000.00	UI	OTH	SC	Anemia
	Zirtec	03/01/2020		Yes	10.00	mg	QD	PO	Chronic Kidney Disease- associated pruritus (CKD- aP)
01-008	zyloric	16/01/2020		Yes	150.00	1/2 cp	ONCE	PO	hyperuricemia
	Cacit	na/na/2019		Yes	2000.00	mg	QD	PO	CKD-MBD
	Vytorin	na/na/2005		Yes	.	mg	QD	PO	Prevention heart attack
	Binocrit	na/na/2019		Yes	6000.00	UI	OTH	SC	Secondary anemia
	Lasix	na/na/2018		Yes	75.00	mg	QD	PO	Hypertension
	Cardioaspirina	na/na/2005		Yes	100.00	mg	QD	PO	Prevention heart attack
	Rocaltrol	na/na/2019		Yes	.	mcg	QD	PO	CKD-MBD
	Lansoprazolo	na/na/2005		Yes	15.00	mg	QD	PO	Gastroprotective
	Amlodipina	na/na/2018		Yes	10.00	mg	QD	PO	Hypertension

Listing 12 - Study IP-001-09 : Previous and Concomitant medications (CM)

Patient no.	Medication	Start date (dd/mm/yy)	End date (dd/mm/yy)	Ongoing	Total dose	Unit	Frequency	Route	Indication
01-009	Eutirox	na/na/2012		Yes	75.00	mcg	OTH	PO	Hypothyroidism
	Cacit	na/na/2019		Yes	2000.00	mg	QD	PO	CKD-MBD
	Cardura	na/na/2017		Yes	8.00	mg	QD	PO	Hypertension
	Mimpara	na/na/2019		Yes	30.00	mg	QD	PO	CKD-MBD
	Lasix	na/na/2017		Yes	50.00	mg	QD	PO	Hypertension
	Eutirox	na/na/2012		Yes	50.00	mcg	OTH	PO	Hypothyroidism
	Peptazol	na/na/2017		Yes	20.00	mg	QD	PO	Gastritis type B
	Dilatrend	na/na/2017		Yes	.	mg	QD	PO	Hypertension
	Mircera	na/na/2019		Yes	75.00	mcg	OTH	SC	Secondary anemia
01-010	Cardura	na/na/2010		Yes	4.00	mg	QD	PO	Hypertension
	Congescor	na/na/2010		Yes	2.50	mg	QD	PO	Hypertension
	Zyloric	na/na/2017		Yes	150.00	mg	QD	PO	Hyperuricemia
	Cacit	na/na/2019		Yes	2000.00	mg	QD	PO	CKB-MBD
	Lasix	na/na/2010		Yes	125.00	mg	QD	PO	Hypertension
	Renagel	na/na/2019		Yes	4000.00	mg	QD	PO	CKB-MBD
	Rocaltrol	na/na/2019		Yes	0.25	mcg	QD	PO	CKB-MBD
	Binocrit	na/na/2019		Yes	6000.00	UI	OTH	SC	Secondary anemia
01-011	Adenuric	na/na/2017		Yes	80.00	mg	OTH	PO	Hyperuricemia
	Renagel	na/na/2019		Yes	1600.00	mg	QD	PO	CKB-MBD
	Nexium	na/na/2017		Yes	20.00	mg	QD	PO	Gastroprotective
	Rocaltrol	na/na/2019		Yes	0.25	mcg	QD	PO	CKB-MBD
	Binocrit	na/na/2019		Yes	6000.00	UI	OTH	SC	Secondary anemia
	Lasix	na/na/2010		Yes	50.00	mg	QD	PO	Hypertension
05-001	Zyloric	na/na/na		Yes	150.00	mg	ONCE	PO	CKD related hyperuricemia
	Coumadin	na/na/na		Yes	5.00	mg	PRN	PO	Atrial Fibrillation
	Antra	na/na/na		Yes	20.00	mg	ONCE	PO	prevention of gastroesophageal reflux
	Norvasc	na/na/na		Yes	5.00	mg	QD	PO	hypertension
	Omnic	na/na/na		Yes	0.40	mg	QD	PO	prostatic hypertrophy
	Rocaltrol	na/na/na		Yes	0.25	mg	QD	PO	CKD related hyperphosphorus
	Kayexalate	na/na/na		Yes	1.00	mis	PRN	PO	CKD related hyperkalaemia
	Totalip	na/na/na		Yes	10.00	mg	QD	PO	hypercholesterolemia
	Sodio Bicarbonato	na/na/na		Yes	1000.00	mg	ONCE	PO	prevention of CKD related acidosis
	Retacrit	na/na/na		Yes	4000.00	UI	OTH	IM	CKD related Anemia
	Normix	10/11/2021		Yes	200.00	mg	QD	PO	prevention of colitis
	Carbonate-Calcium	na/na/na		Yes	2000.00	mg	QID	PO	CKD related hypocalcemia
	Lasix	na/na/na		Yes	250.00	mg	BID	PO	hypertension
05-002	ESKIM	na/na/na		Yes	1000.00	mg	QD	PO	CKD related dyslipidemia

Listing 12 - Study IP-001-09 : Previous and Concomitant medications (CM)

Patient no.	Medication	Start date (dd/mm/yy)	End date (dd/mm/yy)	Ongoing	Total dose	Unit	Frequency	Route	Indication
05-002	NORVASC	na/na/na		Yes	10.00	mg	BID	PO	Hypertension
	Sevelamer	na/na/na	04/11/2021	No	7.20	g	TID	PO	CKD related Hyperfosforus
	DEURSIL	na/na/na		Yes	450.00	mg	QD	PO	biliary lithiasis prevention
	ROCALTROL	27/08/2021		Yes	0.25	MG	QD	PO	CKD related VIT.D shortage
	LANTUS	na/na/na		Yes	5.00	UI	PRN	IM	diabetes
	Cardioasa	na/na/na		Yes	100.00	mg	QD	PO	primary prevention
	Provisacor	na/na/na		Yes	20.00	mg	QD	PO	CKD related dyslipidemia
	RETACRIT	na/na/na		Yes	6000.00	UI	OTH	IM	CKD related anemia
	LASIX	na/na/na		Yes	250.00	MG	BID	PO	CKD
	ferrograd	21/09/2021	04/11/2021	No	105.00	mg	QD	PO	CKD related anemia
	HUMALOG	na/na/na	na/na/na	No	10.00	UI	PRN	IM	diabetes
06-001	renvela	na/na/na		Yes	800.00	mg	TID	PO	hyperphosphatemia
	zemplar	na/na/na		Yes	1.00	mcg	OTH	PO	hyperparathyroidism
	mircera	na/na/na		Yes	150.00	mcg	OTH	SC	anemia
	congescor	na/na/na		Yes	1.25	mg	QD	PO	hypertension
	cardura	na/na/na		Yes	4.00	mcg	QD	PO	hypertension
	lasix	na/na/na		Yes	50.00	mg	TID	PO	diuresis stimolation
	zemplar	na/na/na		Yes	2.00	mcg	OTH	PO	hyperparathyroidism
	mimpara	na/na/na		Yes	30.00	mg	QD	PO	hyperparathyroidism
	zyloric	na/na/na		Yes	100.00	mg	QD	PO	hyperuricemia
	norvasc	na/na/na		Yes	5.00	mg	QD	PO	hypertension
06-002	aranesp	na/na/na		Yes	40.00	mcg	OTH	SC	anemia
	lasix	na/na/na		Yes	75.00	mg	BID	PO	Diuresis stimolation
	loortan	na/na/na		Yes	100.00	mg	QD	PO	hypertension
	renvela	na/na/na		Yes	2.40	g	BID	PO	hyperphosphatemia
	rocaltrol	na/na/na		Yes	0.25	mcg	QD	PO	vitamin D deficiency
	ferinject	na/na/na		Yes	500.00	mg	OTH	IV	iron deficiency
	torvast	na/na/na		Yes	20.00	mg	QD	PO	hypercholesterolemia

Listing 13 - Study IP-001-09 : Bag accountability

Patient no.	Treatment group	Study period	Bags for the patient	Bags used by the patient
01-001	Group B	Day 0 - Day 14	28	28
		Day 14 - Day 28	28	28
01-002	Group B	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14
01-003	Group B	Day 0 - Day 14	28	28
		Day 14 - Day 28	28	28
01-004	Group A	Day 0 - Day 14	16	13
		Day 14 - Day 28	16	13
01-005	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14
01-006	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14
01-007	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14
01-008	Group B	Day 0 - Day 14	28	28
		Day 14 - Day 28	28	27
01-009	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14
01-010	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	0
01-011	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14

Listing 13 - Study IP-001-09 : Bag accountability

Patient no.	Treatment group	Study period	Bags for the patient	Bags used by the patient
05-001	Group B	Day 0 - Day 14	28	28
		Day 14 - Day 28	28	28
05-002	Group B	Day 0 - Day 14	28	28
		Day 14 - Day 28	28	21
06-001	.	Day 0 - Day 14	.	.
		Day 14 - Day 28	.	.
06-002	.	Day 0 - Day 14	.	.
		Day 14 - Day 28	.	.

Listing 14.1 - Study IP-001-09 : Serum L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	43	257	188	63	66
01-002	48	137	107	47	45
01-003	62	262	187	80	63
01-004	36	143	128	59	56
01-005	36	114	77	48	55
01-006	62	190	115	69	86
01-007	119	211	130	76	61
01-008	46	238	206	88	50
01-009	54	203	157	75	70
01-010	42	145	.	.	.
01-011	47	182	161	72	58
05-001	40	229	200	69	53
05-002	20	151	137	52	45
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 14.2 - Study IP-001-09 : Serum Acetyl-L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	5	19	35	6	7
01-002	8	30	24	11	10
01-003	8	62	66	16	11
01-004	9	25	21	9	13
01-005	11	23	12	9	8
01-006	8	14	15	5	9
01-007	19	36	31	11	7
01-008	7	17	32	10	9
01-009	7	33	28	16	10
01-010	8	37	.	.	.
01-011	7	41	39	18	9
05-001	18	79	71	20	19
05-002	8	43	42	13	10
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 15.1 - Study IP-001-09 : Urine L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	46.9	655.3	308.7	5.8	44.1
01-002	23.9	199.5	221.4	27.6	23.1
01-003	58.3	309.5	343.8	69.6	57.6
01-004	42.4	259.3	207.5	64.0	57.4
01-005	14.2	173.0	64.4	16.2	34.2
01-006	57.9	586.9	377.2	131.4	58.8
01-007	171.1	255.8	133.9	16.9	7.8
01-008	11.0	397.3	233.9	32.8	21.9
01-009	90.2	571.0	278.7	30.1	40.8
01-010	60.0	297.1	.	.	.
01-011	17.6	265.3	444.0	21.9	20.6
05-001	9.1	384.6	345.0	43.4	29.6
05-002	3.8	446.1	352.8	59.5	35.4
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 15.2 - Study IP-001-09 : Urine Acetyl-L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	10.8	190.2	72.5	2.5	66.0
01-002	10.3	123.2	101.5	9.6	7.3
01-003	20.8	199.0	124.9	23.2	15.9
01-004	4.1	59.9	66.3	13.3	18.9
01-005	6.8	65.4	13.6	4.6	12.9
01-006	14.0	148.9	121.4	35.0	17.2
01-007	83.7	124.9	84.8	7.9	2.6
01-008	4.0	126.2	85.4	13.1	9.3
01-009	25.1	196.0	96.0	14.1	16.5
01-010	-0.5	-0.5	.	.	.
01-011	8.0	103.6	181.4	9.7	8.1
05-001	3.6	141.5	139.2	19.7	16.7
05-002	1.7	138.1	138.7	22.7	14.3
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 16.1 - Study IP-001-09 : Dyalisate L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	56.4	309.8	180.1	41.2	60.2
01-002	38.3	126.5	317.9	47.1	42.7
01-003	45.2	191.5	172.2	72.9	58.6
01-004	54.4	394.7	107.2	57.0	36.3
01-005	35.1	104.6	73.6	40.8	50.7
01-006	45.6	397.8	98.7	36.8	55.9
01-007	77.9	411.1	96.4	59.4	52.6
01-008	4.7	579.9	175.7	62.0	44.4
01-009	62.3	60.3	143.1	48.7	44.5
01-010	41.8	373.1	.	.	.
01-011	23.1	537.0	147.8	39.4	37.4
05-001	40.6	229.7	196.2	68.3	54.3
05-002	15.2	196.2	148.1	42.4	43.1
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 16.2 - Study IP-001-09 : Dyalisate Acetyl-L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	9.6	27.6	39.9	5.4	9.0
01-002	5.3	30.5	17.6	6.6	6.3
01-003	9.4	61.4	52.6	18.7	11.3
01-004	6.9	9.2	16.4	6.8	5.3
01-005	5.4	18.6	11.0	8.3	9.4
01-006	4.6	7.9	12.0	2.3	5.7
01-007	11.7	23.1	24.6	11.2	7.6
01-008	0.6	18.0	28.2	9.7	9.2
01-009	10.0	9.3	25.1	7.5	5.3
01-010	2.7	17.0	.	.	.
01-011	2.7	18.5	32.6	6.5	5.6
05-001	15.8	67.8	64.4	16.6	15.0
05-002	2.7	30.2	43.8	9.2	7.7
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 17 - Study IP-001-09 : Oxalic acid - Oxalate (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	110.97	36.81	71.14	85.81	36.92
01-002	37.86	87.64	86.25	71.42	14.42
01-003	63.47	91.97	116.75	107.08	23.03
01-004	100.75	100.31	107.81	107.25	113.03
01-005	62.19	62.58	105.36	136.36	83.25
01-006	75.08	139.69	36.97	159.92	98.92
01-007	198.19	245.97	167.14	48.58	78.08
01-008	51.31	61.69	72.03	78.97	57.25
01-009	70.47	77.14	76.97	76.75	51.81
01-010	79.19	104.75	.	.	.
01-011	67.81	68.08	63.81	.	.
05-001	74.98	63.94	53.08	92.94	83.72
05-002	82.78	91.17	78.44	70.61	59.00
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 18 - Study IP-001-09 : Peritoneal equilibration test (PET) - Glucose

Patient no.	Day 0	Day 0 Not Done	Day 28	Day 28 Not done	Day 56	Day 56 Not done
01-001	0.18	No	0.23	No	0.23	No
01-002	0.29	No	0.34	No	0.26	No
01-003	0.27	No	0.30	No	0.24	No
01-004	0.31	No	0.28	No	0.37	No
01-005	0.24	No	0.22	No	0.22	No
01-006	0.27	No	0.27	No	0.31	No
01-007	0.32	No	0.27	No	0.42	No
01-008	0.34	No	0.32	No	0.34	No
01-009	0.23	No	0.28	No	0.29	No
01-010	0.73	No	.	Yes	.	Yes
01-011	0.00	No	0.31	No	0.27	No
05-001	.	Yes	.	Yes	.	Yes
05-002	.	Yes	.	Yes	.	Yes
06-001	.	Yes	.	Yes	.	Yes
06-002	.	Yes	.	Yes	.	Yes

16.1.10 DOCUMENTATION OF INTER-LABORATORY STANDARDIZATION METHODS AND QUALITY ASSURANCE PROCEDURES

This study was conducted with secondary pharmacokinetic endpoints assessed by one centralized laboratory

Local laboratories were utilized for the routine laboratory monitoring stipulated in the protocol. As part of the study initiation procedures, laboratory accreditation and reference ranges were collected for each site.

16.1.11 PUBLICATIONS BASED ON THE STUDY

toxins

MDPI

Article

A New Peritoneal Dialysis Solution Containing L-Carnitine and Xylitol for Patients on Continuous Ambulatory Peritoneal Dialysis: First Clinical Experience

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Abstract: Peritoneal dialysis (PD) is a feasible and effective renal replacement therapy (RRT) thanks to the dialytic properties of the peritoneal membrane (PM). Preservation of PM integrity and transport function is the key to the success of PD therapy, particularly in the long term, since the prolonged exposure to unphysiological hypertonic glucose-based PD solutions in current use is detrimental to the PM, with progressive loss of peritoneal ultrafiltration capacity causing technique failure. Moreover, absorbing too much glucose intraperitoneally from the dialysate may give rise to a number of systemic metabolic effects. Here we report the preliminary results of the first clinical experience based on the use in continuous ambulatory PD (CAPD) patients of novel PD solutions obtained through partly replacing the glucose load with other osmotically active metabolites, such as L-carnitine and xylitol. Ten CAPD patients were treated for four weeks with the new solutions. There was good tolerance to the experimental PD solutions, and no adverse safety signals were observed. Parameters of dialysis efficiency including creatinine clearance and urea Kt/V proved to be stable as well as fluid status, diuresis, and total peritoneal ultrafiltration. The promising tolerance and local/systemic advantages of using L-carnitine and xylitol in the PD solution merit further research.

Keywords: end-stage renal disease; peritoneum; peritoneal dialysis; CAPD; carnitine; xylitol; PD fluid; solution

Key Contribution: End-stage renal disease (ESRD) patients may benefit both locally and systemically from using a glucose-reduced PD solution. Enriching the PD solution with agents such as L-carnitine and xylitol, which have both osmotically and metabolically favorable properties and thereby reduce the intraperitoneal glucose load and exposure, might ensure the peritoneal membrane has a bioactive and more biocompatible glucose-sparing environment without compromising ultrafiltration, residual kidney function (RKF), or uremic solute removal, and independently mitigating the underlying negative systemic metabolic effects

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1. Introduction

There is an increasing worldwide number of end-stage renal disease (ESRD) patients requiring chronic renal replacement therapy (RRT), which represents a significant economic burden on any health system [1]. Peritoneal dialysis (PD) is a consolidated, cost-

effective, home care form of RRT suitable for ESRD, which exploits as its biological dialysis membrane the semipermeable peritoneum [2]. As compared with hemodialysis (the most commonly used dialysis modality), PD is less expensive, has a similar survival rate, preserves residual kidney function better, removes fluid and solutes more gradually and continuously, and cuts right down on cardiac stress [3].

In PD, removal of excess water and retained uremic solutes from the patient's blood (dialytic exchange) occurs through the introduction into the peritoneal cavity, via an implanted intra-abdominal catheter, of a PD solution (also called PD fluid; dialysate). According to the three-pore model, which well describes the peritoneal membrane (PM) function, the capillary endothelium is the membrane's main transport barrier [4]. The PD solution has a usual volume of two liters and contains electrolytes (sodium, magnesium, calcium, chloride), a buffer (lactate and/or bicarbonate), and an osmotic agent in order to remove the daily excess fluid from the patient (peritoneal ultrafiltration, UF) and to enhance convective transport (peritoneal clearance). Following a 4–8 h dwell time, the effluent is drained and fresh dialysate reinfused. One may perform this manually (continuous ambulatory PD; CAPD) via 4–5 daily exchanges, or use an automated cycler (automated PD; APD), usually during the night (a process lasting 8–10 h).

Although PD is a viable treatment for ESRD, it is prescribed in only a minority of dialysis patients [3,5]. The explanation for such a discrepancy lies mainly in certain major limitations concerning PD efficiency and sustainability [6]. In fact, bioincompatibility of the dialysis fluid forms the principal problem for long-term PD patients, since the anatomical and functional integrity of the PM may be impaired [7,8]. Biocompatibility of a PD solution can be defined as the capacity to leave the anatomical and functional characteristics unmodified in time. It can be divided into local (peritoneum cavity) and systemic. Now it is accepted that prolonged exposure to conventional PD fluids is harmful to the peritoneum, causing neoangiogenesis, inflammation, and fibrosis [9,10]. Damage to the PM is indicated by dwindling UF capacity eventually leading to UF failure, the main cause of PD failure [11].

Bioincompatibility in PD is attributed mainly to the high glucose (molecular weight 180 Da) load in the dialysate, the standard osmotic agent used in PD fluid due to its efficiency, low cost, and acceptable safety profile. Currently used PD solutions have a 10- to 50-fold higher glucose content than physiological serum levels; the osmotic gradient thus created makes it possible to remove water, electrolytes, and toxins by UF-associated convection [6]. The effects of such excess glucose, however, include not only a distinct role in the above-mentioned longitudinal changes to the peritoneal membrane but also many potential systemic metabolic effects, including insulin resistance, new-onset diabetes, and cardiovascular disease [12,13].

One of the key objectives of present-day research in PD is to devise strategies to reduce or eliminate glucose-associated toxicity (glucose sparing) without jeopardizing the patient's health. However, finding effective and safe osmotic agents to be used in PD solutions has undoubtedly proved challenging. For PD clinical practice, only two alternative osmotic agents are currently available in glucose-free solutions: the glucose polymer icodextrin and amino acids. These formulations, either alone or in combination, have proved to be effective and PD patients may benefit from their use [14–16]. But icodextrin and amino acids replace no more than 30%–50% of the glucose absorbed every day [12], while they can only be used in a single daily peritoneal exchange [17,18]. Moreover, two recent randomized, controlled studies in PD patients showed that the combined use of icodextrin and amino acids improved metabolic indices, though some patients experienced extracellular fluid volume expansion [19]. The results of these studies emphasize the importance of efficacious UF and the need for close clinical monitoring of the patient's fluid status with any glucose-sparing strategy. We also see from the data and experience published on commercially available glucose-sparing PD solutions (icodextrin, amino acids) that the future of PD depends largely on finding new

osmotic agents improving its biocompatibility and the fluid balance, but also, and no less important, its effect on the metabolism.

The use of osmo-metabolic agents in the PD fluid represents a novel approach to antagonizing glucose-associated toxicity [20]. Osmo-metabolites are substances that have favorable osmotic and metabolic properties [21,22]. The osmo-metabolic approach would ensure a sort of bioactive glucose-sparing both by reducing intraperitoneal glucose load without compromising UF and by the independent mitigation of underlying systemic negative metabolic effects caused by the glucose load. L-carnitine and xylitol represent two such candidate agents. L-carnitine (molecular weight 161.2 Da) is highly water soluble and chemically stable in aqueous solutions [23], which renders it suitable for use in PD fluid. From our previous trials using carnitine-enriched PD solutions, we know the effectiveness of L-carnitine as an efficient osmolyte in PD [24], and that it also enhances CAPD patients' insulin sensitivity [25]. Xylitol (molecular weight 151.2 Da), another osmo-metabolite, is a five-carbon sugar alcohol, pentitol, which is manufactured by the reduction of D-xylulose. A clinical trial many years ago [26] treated six insulin-dependent diabetic patients on CAPD for a minimum of five months using D-xylitol as the sole osmotic agent (three daily exchanges of PD solution with xylitol 1.5% and one exchange with xylitol 3%). Xylitol-containing PD fluid proved safe to use, maintained peritoneal UF, and significantly enhanced the patients' glycemic control (the exogenous insulin dosage was halved, while glycosylated hemoglobin decreased significantly).

Osmo-metabolic agents can be used alone or in combination to maximize their therapeutic effects. We have recently developed a new PD solution containing L-carnitine, xylitol, and a low amount of glucose, and tested its effect on human vein endothelial cells obtained from the umbilical cords of healthy gestational diabetic mothers [22]. Such an experimental PD solution was not associated with the cytotoxicity, inflammation, or nitro-oxidative stress as found with a glucose-based, neutral pH, low-glucose degradation product PD solution, which is regarded as a "biocompatible" solution [27]. Moreover, very recently we compared this innovative PD solution formulation with a wide number of commercial PD solutions (including several "biocompatible" solutions), on human mesothelial cells cultured on inserts and only exposed to the PD solution on the apical side, which is what happens in a PD dwell [28]. The novel PD solutions showed improved performance in terms of cell viability, a better preserved integrity of the mesothelial layer, and less release of proinflammatory cytokines. Our studies also indicate that a little glucose can be retained in the PD fluid, in order to take advantage of its UF ability and energy-providing potential with patients who are often malnourished. Indeed, although the test solutions contained some glucose, it was at a lower concentration and did not seem to have the deleterious effects of the higher concentration [22,28].

Based on these results, the FIRST (efficacy and safety assessments of a peritoneal dialysis solution containing glucose, xylitol, and L-carnitine compared to standard PD solutions in CAPD) study was undertaken. Here we present the results obtained in the first cohort of patients completing the whole study period.

2. Results

2.1. Population Characteristics

Enrollment of eligible patients for the study was greatly hampered and delayed by the COVID pandemic and related implications. The study is currently ongoing. Reported here are the results obtained in the group of patients completing the study period at the Chieti center. Their main characteristics are shown in Table 1. Patients in group A were being treated with a 2.5% glucose dialysate for the nocturnal exchange. Patients in group B were being treated with a 1.5% glucose dialysate for two diurnal exchanges and with icodextrin dialysate for the nocturnal exchange.

Table 1. Characteristics of study population.

	Group A	Group B
Number of patients	6	4
Age (years)	69.8 ± 5.2	55.7 ± 1 2.4
Gender (male/female)	3/3	4/0
Body mass index (kg/m²)	28.8 ± 5.6	28.3 ± 1.2
Systolic blood pressure (mm Hg)	134 ± 22	135 ± 17
Diastolic blood pressure (mm Hg)	82 ± 8	81 ± 10
Heart rate (beats/min)	65 ± 10	77 ± 15
Time on dialysis (months)	6.7 ± 2.6	6.3 ± 0.5

Data are expressed as number or mean ± standard deviation.

During the four-week study period, patients included in group A received a bag with the experimental solution IPX15 for the nocturnal dwell; group B subjects received two bags with the experimental solution IPX07 for the daytime exchanges and a bag with icodextrin solution for the nocturnal dwell. The composition of the experimental bags is detailed in the Material and Methods section. Patients then returned to using their standard solutions in the four-week follow-up period.

2.2. Dialysis Efficiency Parameters

The following efficacy parameters were assessed during the study: total weekly urea Kt/V (a recognized index of dialysis adequacy in general), weekly total creatinine clearance (CrCL), peritoneal equilibration test (PET; a semiquantitative test to provide information about the transport characteristics of the peritoneal membrane), residual kidney function (RKF), daily diuresis, and daily peritoneal UF. The course of the parameters over the study period is shown in Table 2.

Table 2. Parameters of dialysis efficiency during the study period.

Group A			
	Day 0	Day 28	Day 56
Urea Kt/V (weekly)	1.34 (1.12–1.52)	1.42 (1.08–1.57)	1.32 (1.14–1.49)
Net peritoneal UF (mL/day)	175 (0–300)	200 (100–300)	350 (300–500)
Residual kidney function (L/week) *	60.5 (39.0–76.2)	64.8 (46.3–85.9)	48.0 (42.8–78.8)
Creatinine clearance (L/week) *	77.9 (55.5–85.5)	79.9 (55.5–95.8)	62.5 (58.0–91.5)
Solute transport (D/P creatinine)	0.59 (0.57–0.62)	0.62 (0.60–0.66)	0.57 (0.53–0.62)
Solute transport (D/D0 glucose)	0.26 (0.23–0.31)	0.28 (0.27–0.28)	0.30 (0.27–0.37)
Urine output (mL/day)	1425 (1100–2000)	1500 (1100–2000)	1550 (1400–1750)
Group B			
	Day 0	Day 28	Day 56
Urea Kt/V (weekly)	1.41 (1.06–1.52)	1.53 (1.49–1.64)	1.53 (1.49–1.64)
Net peritoneal UF (mL/day)	350 (300–400)	350 (300–400)	400 (350–425)
Residual kidney function (L/week) *	43.0 (38.3–58.3)	45.2 (36.0–65.4)	44.7 (42.1–55.4)
Creatinine clearance (L/week) *	67.4 (62.0–79.6)	67.9 (65.7–84.0)	69.6 (65.3–75.8)
Solute transport (D/P creatinine)	0.60 (0.56–0.64)	0.65 (0.60–0.70)	0.69 (0.60–0.70)
Solute transport (D/D0 glucose)	0.28 (0.23–0.32)	0.31 (0.27–0.33)	0.25 (0.24–0.30)
Urine output (mL/day)	2100 (1925–2150)	1900 (1525–2250)	1825 (1625–2050)

Data are expressed as median (interquartile range). Day 0–day 28, use of the experimental PD solution; day 28–56, use of standard solution. * normalized to body surface area. Abbreviations and definitions: net peritoneal UF, difference between total peritoneal drained volume and total peritoneal filling volume; UF, ultrafiltration; D/P creatinine, dialysate to plasma creatinine ratio during the standard peritoneal equilibration test; D/D0, dialysate glucose concentration ratio between the end and beginning of peritoneal equilibration test.

With regard to small solute clearance, in both groups of patients, Kt/V urea and creatinine clearance showed a slight increase at T28, thereafter declining toward baseline values (group A) or slightly increasing (group B). For residual kidney function, in both groups, a slight increase was found at T28 and a decrease at T56. Mean peritoneal UF in patients of group A proved to be increased at T28 and further increasing at T56, while in group B, peritoneal UF was quite stable. Daily urine volume had slightly increased in group A at both T28 and T56, whereas it proved to be decreased at both time points in group B. Evaluation of PM characteristics by PET showed that patients were average transporters. Small-solute transport, as expressed by D/P creatinine and D/D0 glucose, increased following intervention in both groups, whereas UF during PET showed a slight decrease in group A and a sustained increase in group B patients.

In order to provide a graphical view of the various parameters at the different time points, Figures 1 and 2 show individual data points together with the median of group A and B data lumped together. At first glance, in the overall picture with regard to the changes observed after the intervention and follow-up periods in small solute clearances, PM characteristics and UF were not so dissimilar than groups alone (Figures 1 and 2). The smallest variability was observed in the PM characteristic at all time points, though a greater variability can be seen for the rest of the parameters evaluated, suggesting that more data are necessary to make any firm prediction. The sole significant difference when analyzing data at the three time points proved to be the daily peritoneal UF at T56 when compared to T0 ($p < 0.02$) (Figure 2).

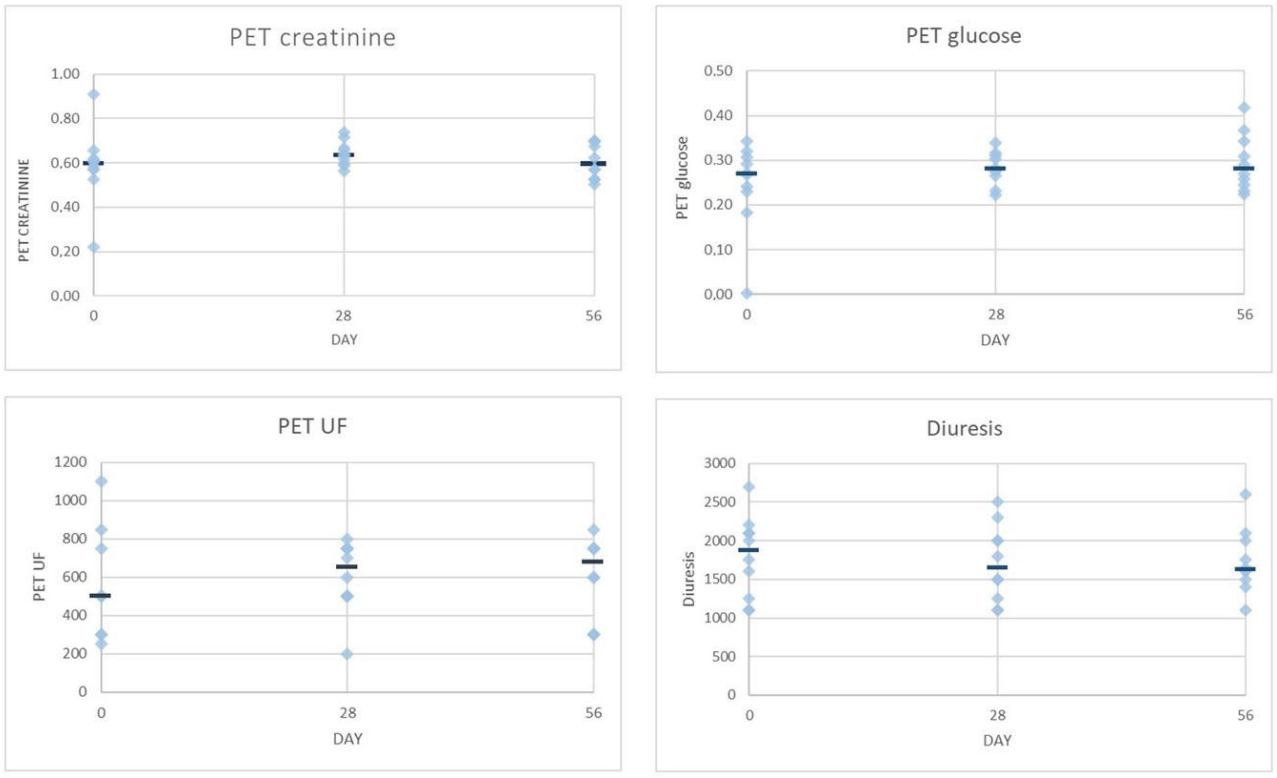

Figure 1. Individual data points and median (-) of peritoneal equilibration test (PET) and diuresis of group A and group B data lumped together. UF, ultrafiltration.

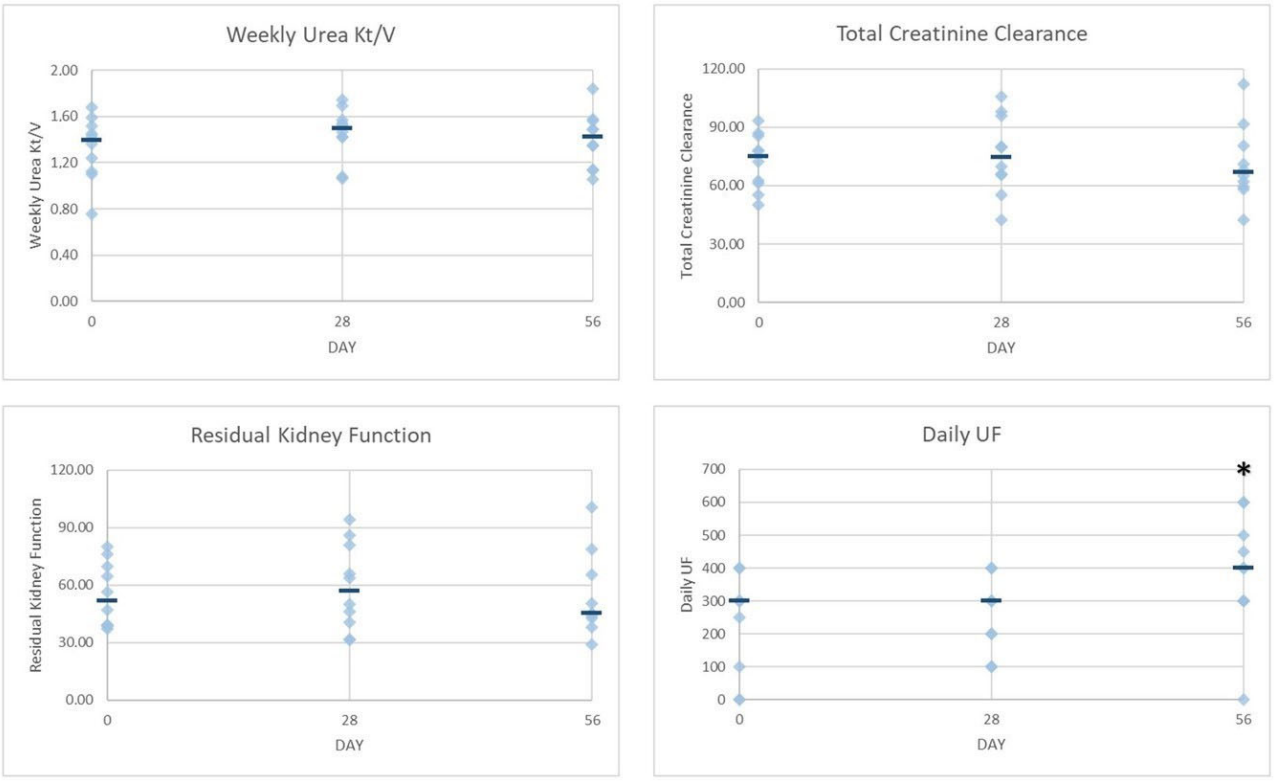

Figure 2. Individual data points and median (-) of dialysis efficiency parameters of group A and group B data lumped together. UF, ultrafiltration. * $p < 0.02$ vs. day 0.

2.3. Safety Results

There was good tolerance of the experimental PD solution, and no patient reported discomfort/pain during infusion. Vital signs, clinical examinations, and electrocardiographic findings did not raise safety concerns. No patient showed any serious signs of overhydration or had appreciable changes in body weight during the study. Medications did not change. The items of the subjective questionnaire on patient's perception of well-being proved to be stable (the score was 18.8 ± 4, 18.3 ± 1.5, 16.5 ± 1.6 in group A and 16 ± 1, 16.5 ± 2.4, 17 ± 4 in group B, at T0, T28, and T56, respectively).

Biochemical parameters showed no significant changes at the different time points of the study (Table S1).

3. Discussion

Peritoneal dialysis is a feasible option for ESRD patients though it has remained underprescribed. This may be due to the high glucose load that current PD solutions cause the patient. The effects of such excess glucose include relatively early limitation of the UF capacity of the PM, and detrimental metabolic effects associated with intraperitoneal glucose absorption. Thus, great efforts are being made to develop alternative PD solutions avoiding these side effects; the aim is to replace part of the glucose content with other osmolytes no less efficient than glucose at removing fluids, but less damaging to the patient's metabolism.

We have recently formulated PD solutions that replace part of the glucose load with other osmotically active metabolites, namely L-carnitine and xylitol [22,28]. This novel osmo-metabolic approach [20] gives the possibility of exploiting the pharmaco-metabolic properties of the two osmolytes to attenuate the systemic side effects due to glucose. Moreover, utilization of a novel PD solution replacing part of the glucose load with osmotically and metabolically active metabolites may give new insights into the potential

positive impact of these novel osmo-metabolic agents on the convective phenomenon occurring in the PM during the continuous PD dwell time or throughout their absorption and effect on biologic pathways of solutes considered to be uremic toxins.

Here we have reported the preliminary results of the first clinical experience using osmo-metabolic agent-based PD solutions in CAPD patients. Use of L-carnitine and xylitol in the PD fluid over four consecutive weeks proved safe and well tolerated in all patients.

Urea Kt/V, creatinine clearance, PET-creatinine, PET-glucose, and RKF are representative of the efficacy of depuration/removal of small molecules through the peritoneal membrane and kidney, whereas diuresis, daily UF, and PET-UF indicate the efficacy of fluid removal through the peritoneal membrane and kidney. With regard to parameters of dialysis efficiency, both creatinine clearance and weekly urea Kt/V seemed to be slightly improved by the end of the intervention period in both group A and group B. Increasing removal of urea may benefit the uremic patient since a number of recent experimental data suggest that urea is toxic at concentrations representative for ESRD [29,30]. RKF seems to follow the same trend as the other dialysis efficacy parameters throughout the study. If further studies confirm that RKF may be longer preserved, uremic toxin removal will be an important advantage achieved by this novel PD solution. It should also be noted that these three parameters were moderately affected by variability of the data (Figure 2).

Interestingly, PM characteristics were much less affected by variability (Figure 1), whereas the PET creatinine seemed to follow the same trend as Kt/V, though PET glucose remained fairly stable throughout the study. If these data were confirmed, it might be speculated that our glucose-sparing solution improves the peritoneal clearance of small solutes without an increase in glucose absorption as expected by Twardowsky [31]. Daily UF did not differ throughout the study in group B, though, after the intervention period, group A showed a slight increase that became more marked by the end of the follow-up, suggesting a sort of carry-over effect. On the other hand, urine output remained fairly stable throughout the study in both experimental groups though with different trends (Table 2). In light of the glucose-sparing approach of our experimental PD solution, it should be noted that patients allocated in group A treated with one exchange of our experimental PD solution (IPX15) received only 20% (10 g vs. 50 g) of the daily glucose load when compared to the traditional glucose-based solution having the same osmotic strength, whereas patients allocated in group B treated with two exchanges of our experimental PD solution (IPX07) received only 30% (20 g vs. 60 g) of the daily glucose load when compared to patients treated with traditional glucose-based solution having the same osmotic strength.

Altogether, our data suggest the noninferiority of the novel solution compared to standard solution as far as adequacy and peritoneal transport characteristics are concerned. However, the results of the present report are clearly preliminary, having been obtained in a small-sized patient population treated for a short period of time, and this is certainly a limitation. The chief causes were difficulty in recruiting eligible patients and the extra intricacies of any controlled clinical trial involving outpatients during the COVID-19 pandemic. Notwithstanding this, the good tolerability and the encouraging data of this proof-of-concept study deserve further investigation in larger and longer studies. These studies are, respectively, ongoing (FIRST trial) or close to start (ELIXIR trial: a six-month randomized study to evaluate the efficacy and safety of XyloCore, a glucose-sparing experimental solution for PD), and will define the role of the proposed novel solutions in daily PD clinical practice.

4. Materials and Methods

4.1. Study Population

Stable patients with ESRD 18 years or older on CAPD therapy for at least three months were recruited in three Italian centers (Nephrology and Dialysis Unit of the

University Hospital of Chieti, Bari, and Rome). Each patient gave written informed consent, and the study was approved by the local Ethics Committee of each center (project identification code IP-001-09; approved on 22/11/2018 by the Ethics Committee of G. d'Annunzio University of Chieti-Pescara, on 9/9/2020 by the Ethics Committee of Bari Policlinico Hospital, and on 5/11/2020 by the Ethics Committee of Rome Policlinico Gemelli).

Prior to entering the study, patients needed to have been regularly treated by CAPD with a standard solution containing 2.5% glucose monohydrate (126.1 mmol/l, Dianeal; Baxter Healthcare, Mc Gaw Park, IL, USA) for the nocturnal dwell (group A), or with 1, 2, or 3 diurnal exchanges according to the patient's need, using standard solutions containing 1.5% glucose monohydrate (75.5 mmol/l, Dianeal) combined with a nocturnal exchange with icodextrin (Extraneal; Baxter Healthcare, Mc Gaw Park, IL, USA) (group B).

Patients were required to be in stable clinical condition for four weeks before the screening period, as certified by medical/surgical history, physical examination, and laboratory exploration. Patients were excluded if they had received L-carnitine or its derivatives in the previous month or experienced a peritonitis episode in the previous three months. Other exclusion criteria included hemoglobin level <9 g/dL, severe diseases or acute infectious conditions, any history of major cardiovascular events like stroke, acute myocardial infarction, coronary, or other arterial revascularization procedures in the last three months before selection, pregnancy or lactation, or life expectancy less than 12 months.

4.2. Study Design

FIRST is a phase II, prospective, investigational, open, multicenter study to investigate the tolerability and the efficacy of a new PD solution containing L-carnitine and xylitol in patients with ESRD receiving CAPD (NCT04001036). The study consists of three study periods (screening, intervention, and follow-up), with a total duration of around 84 days (Figure 3).

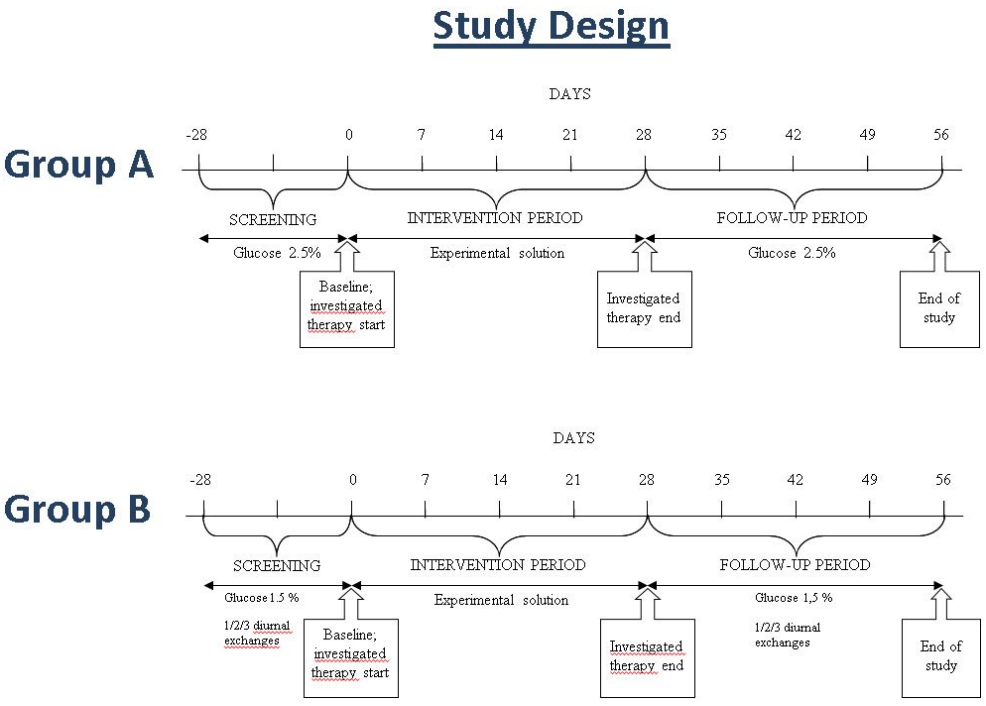

Figure 3. Study design.

After a four-week run-in (screening period), dedicated to the identification of eligible subjects, enrolled patients entered the intervention period, which lasted four weeks. The subjects included in group A received a bag with experimental solution for the nocturnal dwell (IPX15). The subjects included in group B received 1, 2, or 3 bags with the experimental solution for the daytime exchanges (IPX07) and a bag with icodextrin solution for the nocturnal dwell. In the follow-up period of four weeks, patients returned to using standard solution with 2.5% glucose for the nocturnal exchange (group A) or to 1.5% glucose solution for diurnal exchanges and icodextrin for the nocturnal exchange (group B).

Target variables for safety and tolerability assessment of the experimental solutions included patient withdrawal from the study, incidence and severity of adverse events, concomitant medication, abnormal hematology and clinical chemistry measurements, clinical signs of overhydration, and changes in the subjective questionnaire on the patient's perception of well-being.

Since the study has an explorative character, no primary and secondary efficacy parameters were identified. The following efficacy parameters were determined during the study: daily UF volume, weekly total urea Kt/V, weekly total creatinine clearance, and peritoneal equilibration test (PET). The 24 h urine volume was also measured.

4.3. Study Solutions

Study solutions were provided in sterile disposable 2 L bags (Galenica Senese, Monteroni D'Arbia, Siena, Italy). Bags had a pH of 5.5 and the following composition: sodium, 134 mmol/L; calcium, 1.75 mmol/L; magnesium, 0.5 mmol/L; chloride, 103.5 mmol/L; lactate, 35 mmol/L; glucose, 27.7 mM; and L-carnitine, 1.24 mM. Bags differed in their xylitol content: xylitol 98.6 mM (IPX15 solution) or xylitol 46 mM (IPX07 solution). The osmotic strength of our experimental PD solutions was comparable to the glucose-based PD solutions (see above) used before the intervention and follow-up periods. The experimental solutions used in this study were produced in accordance with Good Manufacturing Practice.

4.4. Study Procedures

The study flowchart is reported in Figure 4.

Study Design

		SCREENING PERIOD	INTERVENTION PERIOD		FOLLOW-UP PERIOD	
Day		-28	0	14	28	42	56
Concomitant diseases		x	x	x	x	x	x
Concomitant medication		x	x	x	x	x	x
Clinical parameters [a)]		x	x	x	x	x	x
Functional parameters	Weekly urea KT/V		x		x		x
	PET		x		x		x
	Total creatinine clearance		x		x		x
Carnitine level	Plasma		x	x	x	x	x
	Urine		x	x	x	x	x
	Dialysate		x	x	x	x	x
Total ultrafiltration		x	x	x	x	x	x
Clinical chemistry [b)]		x	x	x	x	x	x
Hematology [c)]		x	x	x	x	x	x
Uric, lactic and oxalic acids		x*	x	x	x	x	x
Electrocardiogram (ECG)			x		x		
Adverse events				x	x	x	x
Subjective questionnaire			x		x		x

Figure 4. Study flowchart. **a**) Clinical parameters include diuresis. **b**) Clinical chemistry: serum sodium, potassium, calcium, phosphorus, total protein, albumin, GOT (AST), GPT (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, glucose, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, blood urea nitrogen (BUN), and creatinine. **c**) Hematology consists of hemoglobin, hematocrit, red blood cell count, white blood cell count and differential, and platelet count. * at day -28, determination of uric acid only.

Peritoneal UF was calculated in the following way: at each dwell, the fresh PD bag was weighed before and after flushing prior to the filling procedure, so as to correct for the flush-before-fill rinsing volume (no fixed volume being used) as well as for any over- or underfilling of the bag. From this last weight, we obtained the volume of infused PD solution by subtracting the weight of the empty bag. We measured the volume of the drained dialysate by weighing the drainage bag and again subtracting the empty bag weight. Peritoneal UF was calculated (mL) as drained (mL) − infused (mL) volume. Residual kidney function and parameters of dialysis adequacy including weekly urea Kt/V and creatinine clearance (defined as residual renal clearance + dialysate clearance) were determined as detailed in Appendix A.

A standard PET was used to assess PM transport characteristics. It consisted of a 4 h dwell with 3.86% glucose during which period we collected dialysate samples at times 0, 120, and 240 min, while a blood sample was taken at 240 min. All blood and dialysate samples were then analyzed within 24 h. The dialysate's creatinine concentration was corrected for interference with glucose in the effluent. The D/P creatinine was calculated as the ratio of dialysate creatinine concentration at 240 min with respect to serum concentration; the D/D0 glucose was obtained as the ratio of dialysate glucose concentration at 240 min to time 0; while the UF volume was gauged from the difference between the 4 h drain and instillation volumes.

All measurements were performed in a fasting state. Blood samples obtained for hematology, clinical chemistry, and uric and lactic acids were analyzed by standard

laboratory techniques. Plasma oxalate was enzymatically determined according to Ladwig et al. [32]. Free L-carnitine and acyl-carnitine esters will be measured in plasma, urine, and peritoneal solution drained out by high-performance liquid chromatography/mass spectrometry [33]. Carnitine measurements are not available yet as, according to the clinical protocol, carnitines determinations will be conducted in a centralized laboratory at the end of the clinical trial.

A subjective questionnaire on patient perception of well-being was also administered. The questionnaire was completed at T0, T28, and T56 and included 15 items: nausea, asthenia, lack of appetite, constipation, diarrhea, stomach pain, muscle aches, muscle cramps, itching, breathing difficulties, chest pain, fatigue, feeling faint, tingling in the hands and feet, problems with the peritoneal catheter. Each item was given a score that ranged from 0 to 5, based on the intensity of the symptom: score 0 corresponded to slight intensity, score 5 to severe intensity. The higher the global score, the worse the perception of well-being.

4.5. Data Analyses

Because of the lack of available data regarding the effects of studied pharmacological association in ESRD patients undergoing CAPD, calculation of sample size was done on the basis of a subjective questionnaire as to the patient's perception of well-being. Forty patients with ESRD treated by CAPD will be included, 20 in group A and 20 in group B.

But for Table 1, data are reported as median (interquartile range). Due to the smallness of the sample (group A, $n = 6$; group B, $n = 4$), the statistical analysis operated with median and interquartile range with the adding of nonparametric repeated measures test (Friedman test) and, if the previous test was significant at the 0.05 level, post hoc Wilcoxon test for the comparison among time points. Scatterplots were used to visualize the distribution of values at the three time points by lumping the data of group A and B evaluated for each parameter in the clinical trial. SAS VERSION 9.4 package (SAS Institute corp., Cary, NC, USA) was used to conduct statistical analyses.

Supplementary Materials: The following are available online at www.mdpi.com/2072-6651/13/3/174/s1, Table S1. Main laboratory parameters.

Author Contributions: Conceptualization, A.A. and M.B.; Data curation, C.R., T.L., and G.D.F.; Formal analysis, J.C.D.-F.; Funding acquisition, A.A.; Investigation, C.R., T.L., and G.D.F.; Methodology, C.R., T.L., and G.D.F.; Software, C.R.; Supervision, L.D.L.; Validation, L.D.L.; Visualization, J.C.D.-F. and M.B.; Writing—original draft, T.L., L.D.L., and M.B.; Writing—review and editing, A.A. and M.B.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the University G. d'Annunzio of Chieti-Pescara (project identification code IP-001-09; approved on 22/11/2018 by the Ethics Committee of G. d'Annunzio University of Chieti-Pescara, on 9/9/2020 by the Ethics Committee of Bari Policlinico Hospital, and on 5/11/2020 by the Ethics Committee of Rome Policlinico Gemelli).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from Iperboreal Pharma (Italy), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Iperboreal Pharma (Italy).

Conflicts of Interest: A.A. is a founder and co-owner of Iperboreal Pharma, an R&D company based in Italy. The other authors declare no conflict of interest. The funder had a role in the design of the study and in the writing of the manuscript; the funder had no role in the collection, analysis, or interpretation of data; or in the decision to publish the results.

Appendix A

Formulas used to calculate residual kidney function and dialysis efficiency parameters

Residual Kidney Function

[(urinary creatinine concentration/serum creatinine concentration) × urinary volume × 7) + (urinary urea concentration/serum urea concentration) × urinary volume × 7]/2
The value obtained was then normalized to the body surface area (BSA):
(residual kidney function × 1.73 m^2 BSA)/patient BSA
BSA = 0.007184 × body weight (kg)$^{0.425}$ × Height (cm)$^{0.725}$ (DuBois formula)

Total weekly creatinine clearance = residual renal creatinine clearance + dialysate creatinine clearance

[(Residual renal creatinine clearance + residual renal urea clearance)/2] + dialysate creatinine clearance
Residual renal creatinine clearance = (urinary creatinine concentration/serum creatinine concentration) × urinary volume × 7
Residual renal urea clearance = (urinary urea concentration/serum urea concentration) × urinary volume × 7
Dialysate creatinine clearance = (dialysate creatinine concentration × serum creatinine concentration) × dialysate volume × 7

The value obtained was then normalized to the body surface area:
Normalized total weekly creatinine clearance = creatinine clearance × 1.73 m^2BSA)/patient BSA

Total weekly urea Kt/V = residual renal Kt/V+ dialysate Kt/V

Residual renal Kt/V: [((urine urea concentration/serum urea concentration) × (urinary volume × 1000/1440)) × 1440 × 7] × body weight (kg) × 0.6 (0.55 if female) × 1000
Dialysate Kt/V: ((dialysate urea concentration/serum urea concentration) × (dialysate volume × 7)) × body weight (kg) × 0.6 (0.55 if female)

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16.1.12 IMPORTANT PUBLICATIONS REFERENCED IN THE REPORT

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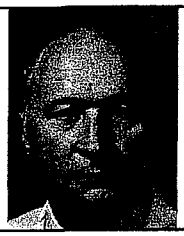

Zbylut J. Twardowski

PERITONEAL EQUILIBRATION TEST

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ABSTRACT

Peritoneal transfer rates of urea, creatinine, glucose, protein potassium, and sodium as well as drain and residual volumes were measured during 103 equilibration tests performed in 18 diabetic and 68 nondiabetic patients. Equilibration test was performed over a 4-hour dwell exchange with 2 L of 2.5% Dianeal solution. Excellent reproducibility was seen after tests were standardized for length of preceding exchange, times of inflow and drainage, patient position, methods of obtaining and processing samples and laboratory assays. Diabetics did not have lower peritoneal solute transfers than nondiabetics. Wide variations were found in the study population.

Measurements of creatinine, glucose and sodium transfer were particularly useful in predicting the patient's response to the standard CAPD. The patients with high-average peritoneal solute transport did well on standard CAPD even after losing residual renal function. Patients with high peritoneal solute transfer rates were likely to have inadequate ultrafiltration on standard CAPD. These patients did much better on dialysis modalities with short dwell exchanges, i.e. nightly peritoneal dialysis (NPD) or daytime ambulatory peritoneal dialysis (DAPD). Patients with low average, and particularly low peritoneal transport rates were likely to develop symptoms and signs of inadequate dialysis as their residual renal function became negligible, particularly in individuals with high body surface area.

Repeated tests were helpful in evaluating causes of insufficient ultrafiltration and/or inadequate dialysis.

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Key Words: Peritoneal equilibration, Peritoneal clearances, Drain volume, Residual volume, Inadequate dialysis, Inadequate ultrafiltration, Dialysate leak, Catheter malfunction, Diabetes, Nightly peritoneal dialysis, Daytime ambulatory peritoneal dialysis, Dialysate laboratory assays.

Dialysate-to-plasma ratios of solute concentrations change at different rates in different patients on peritoneal dialysis (1-3). Peritoneal clearances measured during standard intermittent peritoneal dialysis vary from patient to patient (4-7).

The mass transfer area coefficient (MTAC) was introduced to separate influences of dialysate flow rate and convective transport on solute transfer. This coefficient, based on kinetic models of the solute mass transfer process, is the inverse of peritoneal diffusion resistance and represents the clearance rate, which would be realized in the absence of both ultrafiltration and solute accumulation in the dialysate. This approach has been explored by several investigators (8-13). To determine MTAC, a test exchange is performed with at least two measure-

ments of dialysate and plasma solute concentrations at different dwell times. The MTAC is expressed in ml/min. Results show a very wide variation of MTAC among patients and among studies. Unfortunately, the MTAC measurement is seldom used in routine clinical practice, probably due to the complexity of the calculations.

Since 1983 we have been systematically evaluating peritoneal membrane transport rates by performing an equilibration test. The results are portrayed in a simple, easy to understand, and visually comprehensible method, similar to that of Verger *et al* (14). This paper describes the equilibration test procedures, a retrospective analysis of the results of 103 tests obtained in 86 patients and the usefulness of the test for diagnostic, prognostic, and dialysis planning purposes.

METHODS

General

We began a systematic evaluation of peritoneal membrane transfer rates in November, 1983. For this purpose two liters of 2.5% Dianeal were infused into the peritoneal cavity and serial dialysate samples were taken for urea, creatinine, glucose and protein. Blood samples were taken before and after the test exchange for analysis of the same solutes. After the four-hour dwell, the dialysate was drained and the volume measured. Within a few months most of our patients who were on CAPD had an equilibration test performed at least once. The duration of dialysis before the test ranged from 0.1 to 84 months. Since January 1984, a baseline test was performed shortly after catheter break-in in all new patients entering the peritoneal dialysis program. Based on initial experiences, the test was refined gradually and finally was standardized for length of preceding exchange, times of inflow and drainage, patient position, method of sampling, sample handling, and laboratory assays in October, 1985.

Patients

The study population consisted of 86 patients, aged 19 to 84 years, including 18 with diabetic nephropathy and 68 with other primary renal diseases.

Equilibration test

The final standardized test is as follows: The exchange preceding the equilibration test must dwell for 8-12 hrs. This pretest exchange is completely drained over 20 min in the sitting position, the dialysate is mixed by inverting the bag three times and a dialysate sample is collected. A blood sample is obtained at the end of drainage. A sample of dialysis solution is obtained from the test bag to be infused and a 2 L of 2.5% dialysis solution (Dianeal 2.5%) is infused in portions of 400 ml per 2 min over a total of 10 min. The patient is in the supine position during infusion and rolls from side to side after each 400 ml is infused for better mixing of residual volume and infused solution. Exactly 10 min after the start of infusion, at the completion of infusion (0 dwell time), 200 ml of solution is drained into the bag, mixed well, a 10 ml sample of dialysate is taken and the remaining 190 ml reinfused. The patient is ambulatory during the dwell period. Samples of dialysate are taken with the same technique after 30 min, 60 min, 120 min, and 180 min of dwell time. After a 4 hr dwell time, the dialysis is drained over 20 min with the patient in the sitting position, total volume is measured and a sample taken. The total time of the equilibration exchange is 270 min. A blood sample is obtained at the end of drainage. A sample of dialysis solution is taken from a post-test exchange bag to be infused, and 2 L of fresh solution is infused over 10 min with the same technique as for the equilibration exchange; immediately, 200 ml of dialysate is drained into the bag, a 10 ml sample collected and the remaining 190 ml reinfused.

Chemistries

Serum and dialysate samples were refrigerated at 4°C until assays were done, usually within 1-3 days. Occasionally the samples were frozen. In such instances the samples were thawed at 37°C for 2 hr and mixed vigorously before the assays were run.

Sodium and potassium were measured by ion selective electrode methods on a Nova 1 sodium/potassium analyzer (15). Urea nitrogen was measured by the urease method (16), creatinine by the picric acid method (17), and glucose by the hexokinase and glucose-6-phosphate dehydrogenase methods (18). Serum total protein was measured by the biurette method (19), and dialysate protein by the Coomassie blue dye binding method (20). Urea nitrogen, creatinine, glucose, and total protein tests were performed on an ABA-200 Automated Bichromatic Analyzer (Abbott, Chicago, Illinois). The linearity of assays was checked for all substances within the ranges of values.

Calculations

Corrected creatinine

Glucose interferes with the creatinine assay. In our laboratory, the relationship between glucose concentrations and creatinine readings were linear within the range of 0 – 2500 mg/dl ($r = 0.98$) according to the following formula:

$$\text{creatinine reading (mg/dl)} = 0.000531415\ \text{glucose (mg/dl)} \quad [1]$$

Corrected creatinine was calculated according to the formula:

$$\text{Corrected creatinine (mg/dl)} = \text{creatinine (mg/dl)} - \text{glucose (mg/dl)} \times 0.000531415 \quad [2]$$

The differences between creatinine and corrected creatinine are minimal in blood but are significant in dialysate, especially at short dwell times.

Dialysate to plasma ratios (D/P)

The ratios for urea, creatinine, protein, potassium, sodium, and corrected creatinine at specific dwell times were calculated according to the formula:

$$D/PST = \frac{2\,DST}{PS1 + PS2} \quad [3]$$

Where:

D/PST = dialysate to plasma concentration ratio of solute S at T dwell time.

DST = dialysate concentration of solute S at T dwell time.

PS1 = preequilibration serum concentration of solute S

PS2 = postequilibration serum concentration of solute S

Dialysate glucose at T dwell time (DT) to dialysate glucose at 0 dwell time (DO) concentration ratio (D/DOT) was calculated simply as:

$$D/DOT = \frac{DT}{DO} \quad [4]$$

Residual volumes

Residual volume was defined as the volume of dialysate remaining in the peritoneal cavity after drainage of fluid over 20 minutes.

Residual volume (R) was calculated according to the formula:

$$R = \frac{Vin\,(S3 - S2)}{S1 - S3}$$

where:

Vin = instillation volume

S1 = solute concentration in preinstillation dialysate

S2 = solute concentration in instilled dialysis solution

S3 = solute concentration immediately postinstillation (0 dwell time).

The derivation of the formula is given in the appendix.

The residual volumes by urea, creatinine, glucose, potassium, and protein concentrations were calculated from the pre-equilibration residual volume. The mean values were calculated when residual volumes by all 5 solutes were available.

Statistics

Regression analysis and unpaired t tests were used, where appropriate, to assess the significance of correlations or differences at the $p < 0.05$ level.

RESULTS

Composition of dialysis solution

Table I shows the composition of 2 L 2.5 Dianeal as measured in our laboratory, the assay method used, and the nominal composition of the solution.

TABLE I: *Composition of dialysis solution (Dianeal^R 2.5%)*

SOLUTE ASSAY METHOD	UREA NITROGEN MG/DL UREASE	CREATININE MG/DL PICRIC ACID*	GLUCOSE MG/DL HEXOKINASE	PROTEIN MG/DL COOMASSIE	SODIUM MEQ/L ELECTRODE	POTASSIUM MEQ/L ELECTRODE
N	74	78	77	78	79	77
X	0.1757	1.1359	2137.5	0.0000	131.32	0.2286
SD	0.3831	0.2553	97.8	0.0000	2.64	0.1830
Minimum	0.0000	0.6000	1800.0	0.0000	125.00	0.0000
Maximum	1.0000	2.6000	2363.0	0.0000	140.00	0.6000
Nominal	0.0000	0.0000	2272.7†	0.0000	132.00	0.0000

*Glucose interferes with picric acid assay for creatinine. Each mg% glucose overestimates creatinine concentration in dialysate by:

$$\frac{1.1359}{2137.5} = 0.000531415\ \text{mg/dl}$$

†Dianeal^R 2.5% is prepared by dissolving 2.5 wt% of hydrated glucose with molecular weight of 198 daltons, thus, the concentration of anhydrous glucose is:

$$\frac{180}{198} \times 2500\ \text{mg/dl} = 2272.7\ \text{mg/dl}$$

The major differences between nominal and measured concentrations are in creatinine and potassium; minor differences are in glucose and sodium. Protein was never found by the Coomassie method; however, urea was measured in three samples at concentrations of 1 mg% by the urease method.

Dialysate to plasma ratios (D/P)

Figures 1 and 2 present the means, standard deviations, minimal and maximal values at all dwell times for urea, creatinine, protein, corrected creatinine, potassium, and sodium. The ranges of values are the lowest for urea and potassium and the highest for protein. Tables with exact values are reported elsewhere (21).

Dialysate glucose

Figure 2 shows the ratios for dialysate glucose concentration at particular dwell time to dialysate glucose at 0 dwell time; the values are presented in similar format to those of D/P.

Drain volumes

Figure 2 portrays the results of drain volumes. The range of drain volumes was very wide. Most patients with drain volumes below 2000 ml had subcutaneous leaks during the test, which were documented later and one patient had an excessive lymphatic

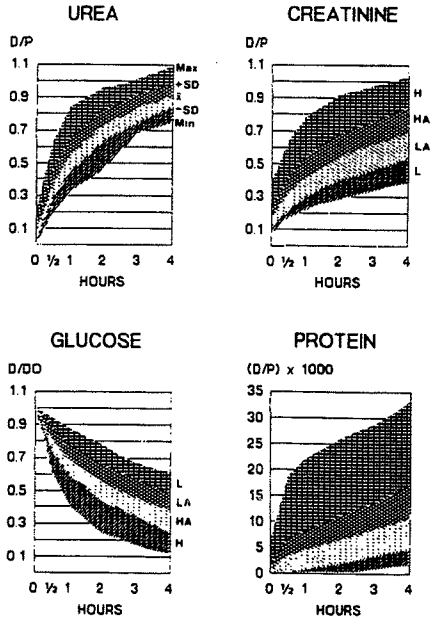

Figure 1: *The equilibration test results in the study population. Areas shaded in different patterns portray results representing high (H), high average (HA), low average (LA), and low (L) peritoneal transport rates. For urea, creatinine and protein, the higher dialysate-to-plasma ratio (D/P) the higher the transfer rate; because glucose transport direction is opposite to that of other solutes, the higher the concentration ratio of dialysate glucose at particular dwell time to dialysate glucose at 0 dwell time (D/DO) the lower the transfer rate. Areas of high, high average, etc., transfer rate categories for urea and protein, have the same shade pattern as those for creatinine. Maximal, mean (1SD, mean, mean – 1SD, and minimal values border the four categories.*

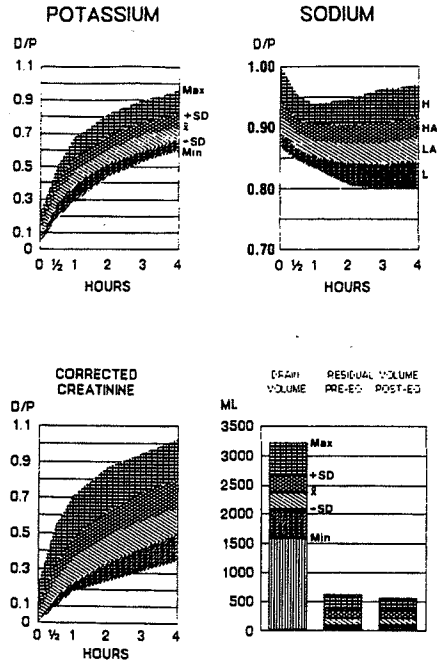

Figure 2: *The equilibration test results in the study population. Areas shaded in the same pattern represent the same category of transfer rate, drain volume, and residual volume. See legend to Fig 1 for further explanation.*

absorption of fluid (22); very high values were found in patients with incomplete drainage of the pre-equilibration exchange as judged by a high pre-equilibration residual volume and a low postequilibration residual volume. The drain volume results showed less variation after the test was standardized (Table II).

Residual volumes

Table II presents residual volumes as calculated by glucose, potassium, urea, creatinine, and protein, as well as the mean residual volumes calculated by all five solutes in last 22 tests where the procedure was standardized. Figure 2 presents the results of mean residual volumes in all tests, including those before test standardization.

Categorizing the patient according to the peritoneal solute transport rates, drain volumes, and residual volumes

For each solute the transport rate was categorized as low, low average, high average, and high (Figs 1 and 2). A low transport rate was defined as a D/PS ratio < mean − 1SD or a D/DO > mean + 1SD. Low average transport was defined as a D/PS between the mean – 1SD and the mean, or a D/DO between the mean and the mean + 1SD. High average transport was a D/PS between the mean and the mean + 1SD or a D/DO between the mean − 1SD and the mean. A high transport rate was present if D/PS was > the mean + 1SD or D/DO was lower than the mean − 1SD. The curve of an individual test was categorized according to the position of at least two points at 2, 3, and 4 hr dwell time.

Drain volumes and residual volumes were categorized using the same principle as for dialysate to plasma ratios (figure 2).

Reproducibility of equilibration curves

The tests were repeated in patients who had inadequate dialysis, inadequate ultrafiltration, or unexpected changes in serum chemistries. The tests were repeated once in 11 patients and twice in three patients.

We assumed that the peritoneal transport characteristics did not change significantly for clinical purposes if D/PS and D/DO ratios did not differ for more than one standard deviation from those in previous tests.

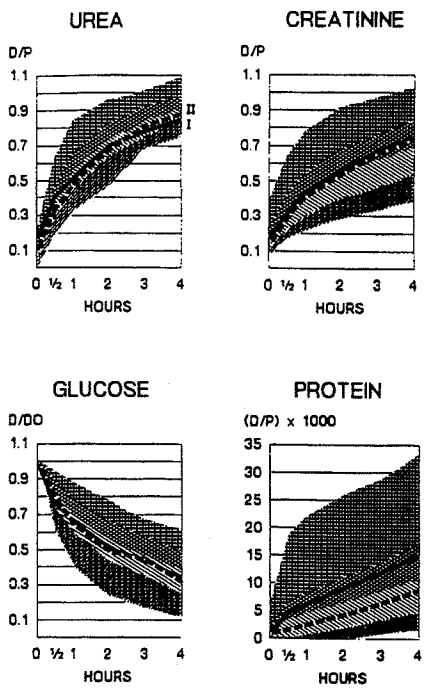

Figure 3: *Repeated equilibration tests in a patient who reported insufficient ultrafiltration are superimposed on the study population results. The curves for urea, creatinine, and glucose are almost identical in both tests and fall within the high average category for creatinine and glucose. The differences in curves for protein depend on the different length of the preceding exchange, which was longer before the first test than before the second. The first test is indicated by a solid line, the second by a dashed line.*

Figures 3 and 4 show the results of repeated tests in a patient within a time span of 10 months. All results were similar except for protein dialysate-to-plasma ratios, which were lower on the repeated test. The second test was performed after a short dwell (3 hr) exchange, the first test after a long (12 hr) exchange. The length of a preceding exchange markedly influences protein

TABLE II: *Residual volumes calculated by five solutes and drain volumes in last 22 tests where the procedure was standardized*

	RESIDUAL VOLUME (ML) MEAN												DRAIN VOLUME AFTER 4 HOUR DWELL (ML)
	PREEQUILIBRATION						POSTEQUILIBRATION						
SOLUTE	GLUCOSE	POTASSIUM	UREA	CREATININE	PROTEIN	MEAN OF FIVE	GLUCOSE	POTASSIUM	UREA	CREATININE	PROTEIN	MEAN OF FIVE	
N	22	22	22	22	22	22	22	22	22	22	22	22	22
Mean	221	244	230	214	116	206	244	213	212	199	78	193	2463
SD	135	124	120	99	127	102	162	116	116	97	110	106	199
Minimal value	23	67	0	32	0	35	12	61	0	51	0	63	1980
Maximal value	444	592	519	465	520	413	540	560	500	400	370	388	2740

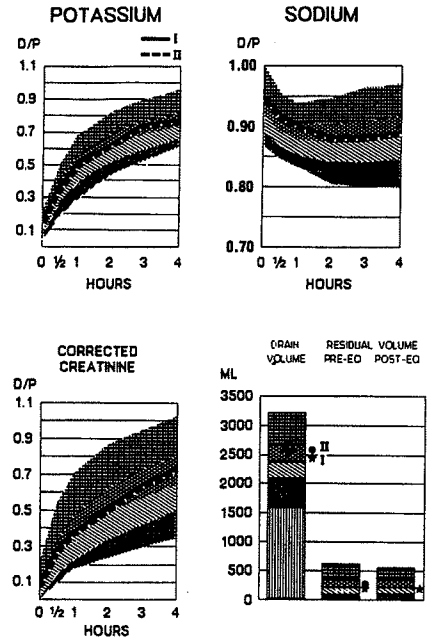

Figure 4: *Repeated equilibration tests in the same patient as in Fig 3 are superimposed on the study population results. The results are almost identical in both tests, drain volumes are high average, residual volumes are average. A reported "inadequate" ultrafiltration was due to dietary indiscretions.*

D/P ratios but influences less the ratios of other solutes. Such findings led to standardization of a preceding long dwell exchange.

Figure 5 portrays the results in a patient with long dwell exchanges before both tests. All results, including protein, are close to each other.

Figure 6 shows another example of the discrepancy in protein curves, whereas other curves are closer to each other. The patient was off dialysis for 8 hrs before the first test, whereas the second test was performed after a short (4 hrs) exchange. The slopes of protein D/P ratios are not different from 1 – 4 hr dwell times but the curve with no preceding exchange is shifted upwards. The closest results in both tests were obtained for creatinine.

Stability of curves over time

Thirteen patients showed stable peritoneal membrane transport characteristics on repeated tests according to our definition; seven had results almost identical, similar to those shown in Figs. 3-5. Three patients had higher transport rates, three patients had lower transport rates but within the limits of 1 standard deviation. Only one patient showed clinically significant changes in peritoneal transport characteristics. Figure 5 shows the results in this patient. On the first test, done shortly after transplant rejection, the results fall within the low average category. This patient, with complete anuria and a body surface area of 2.11 m^2, had serum creatinine values of 23.8 mg/dl on four 2 L exchange schedule. After switching to four 3 L exchanges the serum creatinine dropped to 17.5 mg/dl and was stable for six months, then gradually dropped to 13 mg/dl. On repeated tests there was a significant increase in peritoneal transport of all solutes (Fig. 7). The patient was switched back to four 2 L exchange schedule, serum creatinine rose to and stabilized at 16-17 mg/dl. No reason for the change in peritoneal transfer rates could be revealed.

Sudden loss of ultrafiltration

Figure 8 shows the results in a patient with a sudden loss of ultrafiltration. The other results of the same patient are portrayed in Fig. 5. The peritoneal

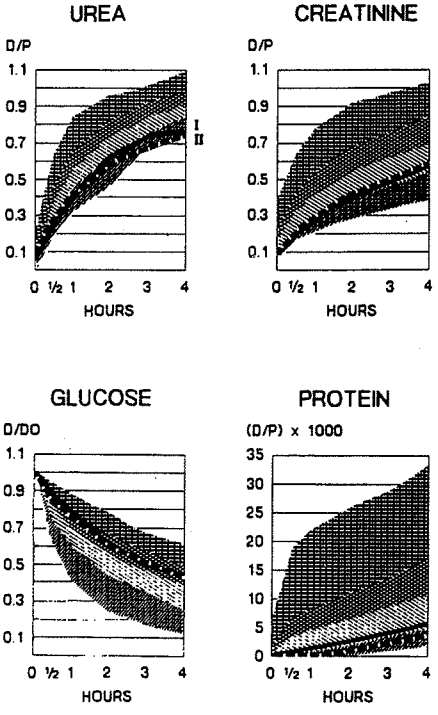

Figure 5: *The equilibration curves in a patient who had long dwell exchanges before both tests are related to the population studies. The curves in the repeated test (dashed line) are almost identical to those in the first one (solid line).*

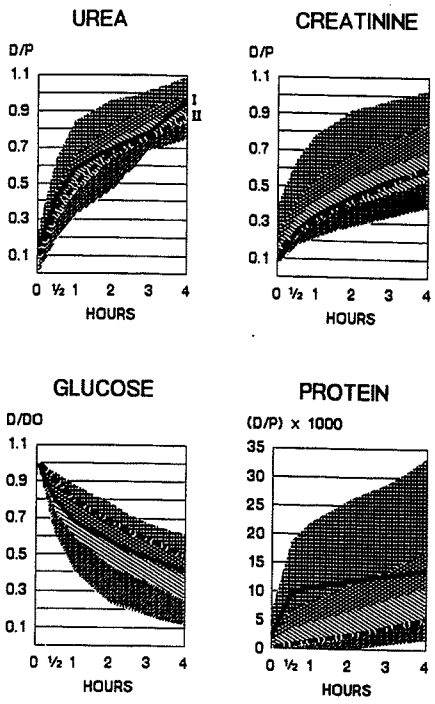

Figure 6: *Markedly higher protein dialysate-to-plasma ratios during the first test (solid line) without a preceding exchange compared to those during the second test (dashed line) with a short preceding exchange. The slopes of both curves for protein are parallel from 1 to 4 hour dwell time, but the first curve is shifted upwards. The curves for creatinine are least influenced by the presence or absence of a preceeding exchange.*

transport characteristics are almost identical, residual volumes were low yet the drainage volume dropped significantly. These results are typical for a dialysate leak. The patient regained ultrafiltration ability after two weeks of hemodialysis.

Inadequate dialysis

Eleven patients required high-volume dialysis (four 2.5 L exchanges; high volume CCPD; four 3 L exchanges) one patient required hemodialysis to eradicate symptoms of inadequate dialysis on standard modalities (4 × 2 L, 3 × 2.5 L, or 3 × 3 L exchanges); at the time of change in therapy, the urine output dropped below 300 ml/day. In these patients, the maximum D/P values of creatinine, sodium, and corrected creatinine were below means for the population, but were above means for other solutes in 3 patients. Thus, the patients with transport rates below the population means for creati-

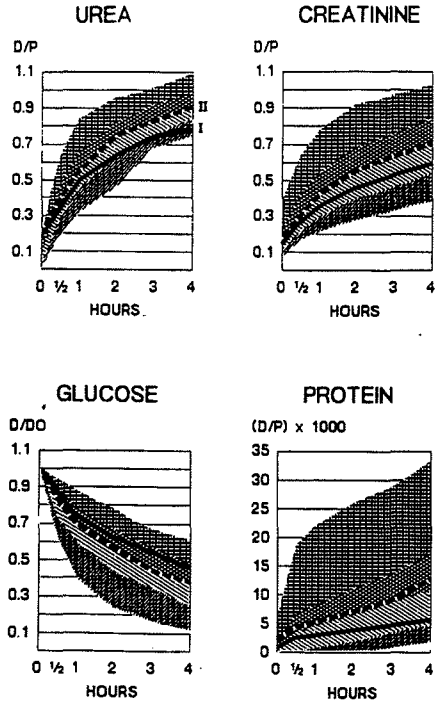

Figure 7: *The repeated equilibration test (first in solid, second dashed) in a patient with significant increase in the peritoneal solute transport are related to the population studies.*

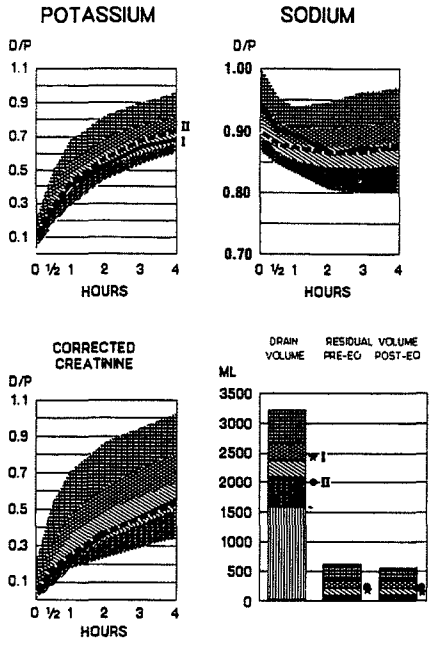

Figure 8: *Repeated equilibration test in the same patient as in Fig 5 related to the population study. This patient reported a sudden loss of ultrafiltration. The only difference between the two tests is in the drainage volume, which is lower in the second test. Such results are typical for a dialysate leak. Although a leak site could not be localized, the patient regained ultrafiltration ability after two weeks of hemodialysis. This supports the diagnosis.*

nine and sodium are likely to develop symptoms of inadequate dialysis, particularly if the body surface area is above 2.0 m^2 and residual urine output becomes negligible.

Inadequate ultrafiltration

Five patients had permanently inadequate ultrafiltration and had to be switched to nightly peritoneal dialysis (NPD), daytime ambulatory peritoneal dialysis (DAPD) ("nights off dialysis") or hemodialysis. The transport rates were high for all solutes, except of urea and potassium which were high average in one patient.

Diabetics vs nondiabetics

Diabetic and nondiabetic patients had similar results after the equilibration test except for dialysate-to-plasma ratios for urea and creatinine, which were higher in diabetics. The differences were small, although some of them were statistically significant (Fig. 9).

Correlations

Excluding creatinine vs corrected creatinine (r = 0.996), the best correlations were D/P ratios for corrected creatinine vs sodium (Fig. 10), corrected creatinine vs glucose (r = −0.945), and creatinine vs glucose (r = −0.925). The best correlations with drain volume were inverse correlations with D/P sodium (Fig. 11) and creatinine and positive correlation with D/DO glucose (Fig. 12). Potassium and urea transport rates were not significantly correlated with drain volumes (r = −0.216, $p > 0.1$; and r = −0.121, $p > 0.2$ respectively). This observation supports previous reports that the ultrafiltration rate is dependent on many factors and that high membrane permeability to glucose is only one reason for poor ultrafiltration at 4 hr dwell time. The patients with low peritoneal transport rates have low dialysate sodium concentrations due to molecular sieving and slow diffusion. Interestingly, the excellent correlations between sodium dialysate-to-plasma ratios vs transport rates of corrected creatinine (Fig. 10) and glucose are in contrast with rather poor correlation with drain volumes (Fig. 11). Sodium sieving reflects the generation of ultrafiltrate but net drain volume is the result of the ultrafiltrate generation *minus*

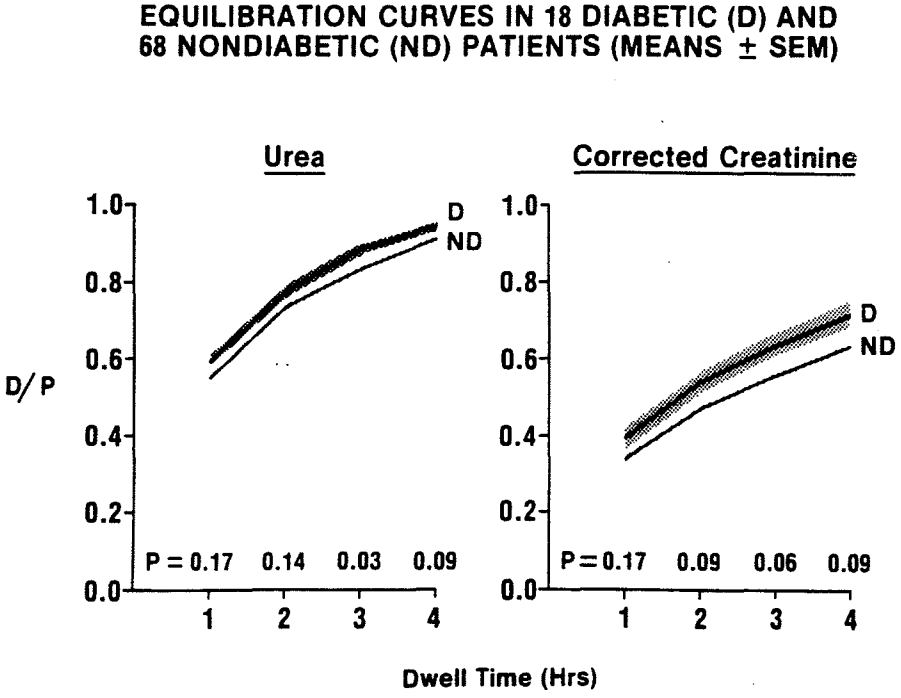

Figure 9: *Means ± SEM of dialysate-to-plasma ratios for urea and creatinine in diabetic and nondiabetic patients. The differences in values are small, although some are significantly higher in diabetics.*

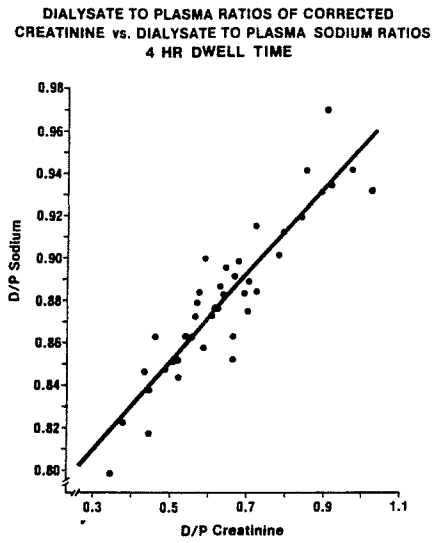

Figure 10: *The correlation of dialysate-to-plasma ratio of corrected creatinine at 4 hour dwell time vs dialysate-to-plasma ratios of sodium at 4 hour dwell time (r = −0.956).*

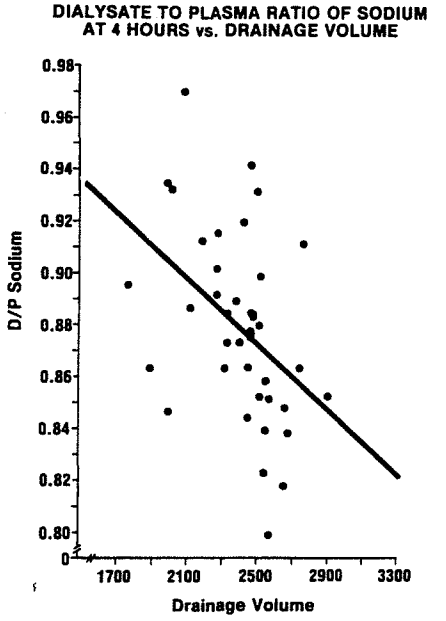

Figure 11: *The relationship between dialysate-to-plasma ratios of sodium at 4 hour dwell time and drain volumes (r = 0.546).*

dialysate absorption through the lymphatics, eventual dialysate leak and/or incomplete drainage.

Mean solute transport rates and drain volumes were unchanged with time on dialysis (all $r < 0.2$; $p > 0.1$); however, the highest ranges of values were observed shortly after the beginning of dialysis. As an example, the dialysate-to-plasma ratios of corrected creatinine at 4 hr dwell time vs time on dialysis is portrayed in Fig. 13. Most patients who stayed on a regular dialysis schedule belonged to the high average peritoneal transport rate category. We hypothesize that the figure portrays the process of natural selection. Most patients with high or low values transferred from CAPD and were not available for a cross-sectional study in 1983. In 1983 alternate forms of peritoneal dialysis became available in our center. Eleven patients with low or low-average peritoneal transport characteristics had to be switched to high flow dialysis because of inadequate dialysis, four with high transport rates were switched to nightly peritoneal dialysis or daytime ambulatory peritoneal dialysis because of inadequate ultrafiltration. One patient was switched to hemodialysis because of inadequate ultrafiltration, even on nightly peritoneal dialysis. This last patient had excessive lymphatic absorption as reported elsewhere (22).

DISCUSSION

Standard CAPD with four 2 L exchanges/day is the most widely used form of peritoneal dialysis at present; however, after two years of therapy, almost 34% of patients are transferred from CAPD (23). Although, frequent peritonitis is the main single reason for dropout, over 70% of transfers are related to other medical and psychosocial problems (23).

Newer modifications of peritoneal dialysis such as continuous cyclic peritoneal dialysis (24), nightly peritoneal dialysis (25), and high volume peritoneal dialysis (26), allow continuation of peritoneal dialysis in patients who cannot continue on a standard regimen due to inadequate dialysis or inadequate ultrafiltration (27). The peritoneal transport rate is an important factor in determining the patient response to various forms of peritoneal dialysis.

Although, the variation in peritoneal transport rates among patients has been recognized since the early days of peritoneal dialysis, this has not attracted deserved attention for diagnostic, prognostic and dialysis planning purposes.

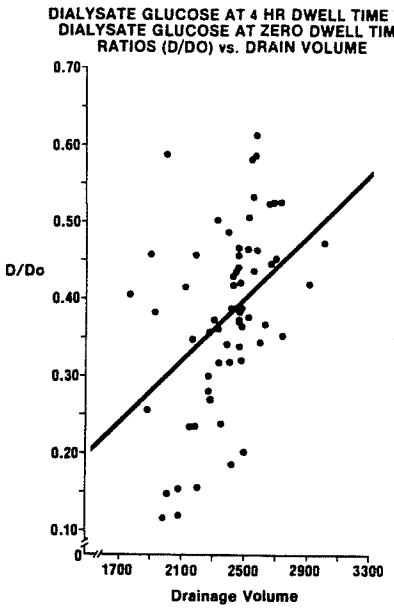

Figure 12: *Ratios of dialysate glucose at 4 hour dwell to dialysate glucose at 0 dwell are correlated with drain volumes (r = 0.434).*

We believe that there were at least 3 reasons for this failure: 1) the reproducibility of the results was unsatisfactory, 2) different solutes showed different results in individuals, and 3) the method of presentation as MTAC was not readily accepted because of the complexity of calculations. To overcome the last problem, Popovich and Moncrief (28) published a nomogram to calculate MTAC from a single measurement of solute dialysate-to-plasma ratio at specific dwell time. We do not think that such a recalculation is necessary. The simple D/P ratios is as good as MTAC and is more likely to be clinically accepted.

To achieve a satisfactory reproducibility of results, the procedure must be standardized. The length of the preceding exchange influences dialysate-to-plasma ratios, particularly protein. This influence is best illustrated in Fig. 6. Before the first equilibration test, the patient was off dialysis for 8 hours. Protein that had accumulated in the "ascitic fluid" did not immediately mix completely with the infused solution; therefore, the measured concentration of protein in the sample at 0 dwell time was low; however, after 60 mintues of dwell time, the dialysate was well mixed and the protein concentration was markedly higher. The protein

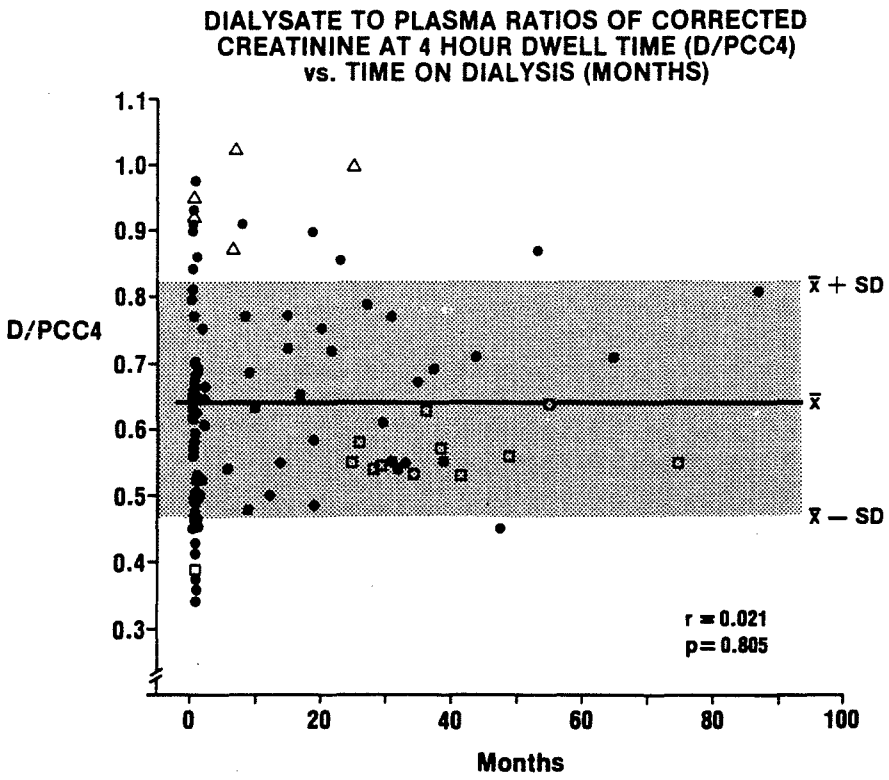

Figure 13: *Dialysate-to-plasma ratios of corrected creatinine at 4 hour dwell (D/PCC4) vs time on dialysis (months). Shaded area represents values between + and − 1 SD from the mean. Closed circles represent values in patients who remained on standard CAPD (dialysis solution inflow < 9 L/day), open triangles represent values in patients with inadequate ultrafiltration, open squares represent values in patients with inadequate dialysis. Only values of the latest equilibration test in a patient are depicted. After 20 months of dialysis only a few patients with values outside shaded area remained on standard CAPD.*

concentration at one hour dwell time represents the protein in residual volume and protein transported during the dwell. At longer dwell times, the slope of the curve represents only an increase in protein concentration due to the transport during the dwell. With a short preceding exchange before the second equilibration test, the protein content in residual volume was low, therefore the slope of the curve is linear from 0 dwell time, because it represents almost exclusively protein transfer from the beginning of the dwell without significant influence of the residual volume protein.

Handling of samples is also extremely important. If dialysate is frozen, the samples have to be thoroughly thawed, preferably at 37°C for at least 2 hr and well mixed before runs. Although, it should be common knowledge that sample problems arise during freezing and thawing, many analysts are not aware of this. Omong and Vellar (29) found the highest concentration of solutes at the bottom of tubes after thawing. This phenomenon is produced during thawing, when more concentrated solution thaws first and runs down to the bottom along the tube walls. Simple inversion of tubes is not sufficient. The sample should have additional mixing on a vortex. The error due to incomplete mixing is more likely in dialysate than in the serum because of high osmolality of the former. Because of wide ranges of dialysate values, the linearity of assays must be checked beyond the routine ranges recommended by the manufacturer. Methodology must be adjusted and/or samples diluted before testing.

The dialysate-to-plasma ratios of urea and creatinine were slightly higher in diabetic than in non diabetic patients (Fig. 9). Although the differences were mostly insignificant, the ratios were definitely not lower in diabetics. In contrast to a previous case report (30), we may safely say that diabetic patients in general do not have peritoneal transport rates lower than nondiabetic patients.

Most patients have stable transport rates as judged by repeated equilibration tests and clinical observations; however, in some patients the transport rate does change.

Delineation of a patient's peritoneal transport rate is useful clinically. Although there are significant correlations between transport rates for different solutes, the best correlations are between creatinine and glucose, glucose and sodium, and creatinine and sodium. Also, creatinine (or corrected creatinine) transport rates show the best correlations with clinical responses of the patients to peritoneal dialysis. The patients with high average transport rates have adequate dialysis and ultrafiltration on standard schedules of four 2 L exchanges, even after the residual renal functions become negligible. The patients with high transport rates of creatinine, glucose, and sodium require high dialysis-solution glucose concentration and, after losing residual renal functions, frequently are not able to continue on the standard CAPD (Fig 13) due to poor ultrafiltration.

The higher the transport rate the more benefit to ultrafiltration from short, frequent exchanges that maintain high dialysate-to-plasma glucose concentration ratios and capture peak ultrafiltration when dialysate glucose concentration is still high. Dialysate sodium concentration is high in these patients, thus, sodium balance is adequate. Figures 1-2 show that D/P ratios for small-size solutes in patients with high peritoneal transport rates are higher at 1 or 2 hr dwell time than the ratios at 4 hrs in patients with low peritoneal transport rates. Thus, the same clearances can be achieved in 50-75% shorter time in patients with high transport rates than in patients with low transport rates, provided the number of exchanges remains the same. These patients are ideal candidates for NPD or CAPD.

Patients with low average peritoneal transport rates of creatinine (or corrected creatinine) are likely to develop symptoms of inadequate dialysis after

losing residual renal functions (Fig. 13), particularly if the body surface area is above average. These patients frequently require higher volums exchanges or even combinations of NPD and CAPD (27). These patients usually have excellent ultrafiltration on CAPD.

Patients with low peritoneal transport rates are even more likely to develop symptoms of underdialysis on a standard CAPD schedule. Figures 1-2 show that, in patients with low peritoneal transport rates, the D/P and D/DO raios show almost linear changes during dialysate dwell. Small molecules in these patients behave like middle molecules in patients with high peritoneal transport rates. In these patients, frequent exchanges have only moderate effect on clearances. Sodium sieving is more apparent (low ultrafiltrate sodium) and inadequate sodium balance may be expected with shorter exchanges (25). These patients are not good candidates for NPD. If NPD is required for various reasons, the duration of treatment must be markedly longer than in patients with high peritoneal transport rates (25, 27). Dialysis solution sodium concentrations <132 mEq/L may be required in these patients.

Mean residual volumes as calculated by five solutes were close to 200 ml, markedly lower values than 923 ml reported by Chandron and Flynn (31) as calculated by potassium. In our studies, residual volumes calculated by potassium were only slightly over 200 ml (Table II). Chandron and Flynn assumed that the potassium concentration in dialysis solution is 0, which is not the case according to our study. Also, in the previous study, the dialysate sample was taken 5 min after instillation (we sampled immediately after instillation). Thus, a longer diffusion time overestimated the results. The differences in methodology may explain the discrepancy in the results.

The calculation of residual volumes are based on the assumption that the mixing of fluid in the peritoneal cavity is instantaneous and complete, that there is no diffusion of a solute after drainage of the preceding exchange, during infusion, and during sampling at 0 dwell time. Also, it is assumed that the laboratory assay is precise. These assumptions are not entirely correct. The precision of the sodium measurement is not sufficient for the requirement of a residual volume calculation, because the values are too close to each other, resulting in unacceptable variation. Laboratory imprecision in measurements influences the results less if the differences between values are higher. Also, the diffusion of solutes is slower if the solute concentration in dialysate is close to equilibration with plasma. Therefore, the results after long dwell exchanges are more consistent. For small-molecular-weight solutes, incomplete mixing is counterbalanced by diffusion during the infusion and sampling. Poor mixing of protein is not counterbalanced by significant diffusion; therefore, the values calculated for protein were the lowest.

The measurement of residual volumes is of limited usefulness. Only high deviations from the means indicate poor drainage. Catheter malfunction may be easily diagnosed with simpler methods like measuring the outflow rate or assessing the position of the catheter on an abdominal x-ray.

Most useful in predicting patient responses to peritoneal dialysis were dialysate-to-plasma ratios of creatinine (or corrected creatinine), sodium, and D/DO ratios at 2, 3, and 4 hr, which indicates the possibility of performing a simplified equilibration test. The simplified test can be performed as described in the methods; however, only one blood sample for creatinine is taken after a 2 hr dwell time, and dialysate samples are taken at dwell times 0, 2 hrs, and 4 hrs, only for glucose and creatinine. Even one dialysate sample for creatinine at 2 hrs or 4 hrs dwell time would be sufficient to categorize the patient into a particular transport rate group. Additional samples for creatinine and glucose serve as controls. In case of incompatibility in the results, the test would need to be repeated or the unabridged test would be required.

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APPENDIX

Derivation of the Formula to Calculate Peritoneal Residual Dialysate Volume

The amount of a solute in the peritoneal cavity after a complete drainage (in the residual volume) equals:

$$R\,S1 \quad [1]$$

where: R = residual volume

S1 = solute concentration in residual volume. It is assumed that this concentration is the same as in the preinstillation (drained) dialysate.

Immediately after instillation of the fresh dialysis solution the amount of a solute present in the peritoneal cavity equals:

$$R\,S1 + Vin\,S2 \quad [2]$$

where: Vin = instillation volume

S2 = solute concentration in instilled dialysis solution

Assuming a complete mixing of instilled dialysis solution with the residual volume and no diffusion to or from the peritoneal cavity during infusion and sample taking, the amount of a solute present in the peritoneal cavity equals also:

$$(R + Vin)\,S3 \quad [3]$$

where: S3 = solute concentration immediately post instillation in a sample taken at 0 dwell time

$$\text{Thus, } R\,S1 + Vin\,S2 = (R + Vin)\,S3 \quad [4]$$

$$\text{or } R\,S1 + Vin\,S2 = R\,S3 + Vin\,S3 \quad [5]$$

$$\text{and } R\,S1 - R\,S3 = Vin\,S3 - Vin\,S2 \quad [6]$$

$$R(S1 - S3) = Vin(S3 - S2) \quad [7]$$

$$R = \frac{Vin(S3 - S2)}{S1 - S3} \quad [8]$$

The mean volume of 2 L 2.5% Dianeal is 2,080 ml. Because 10 ml sample was taken from the bag prior to infusion, a value of 2,070 ml was used for Vin.

16.1.13 DSMB Charter, Meeting Minutes

Not applicable

16.2 SUBJECT DATA LISTINGS

Study **IP-001-09**

Efficacy and safety assessments of a peritoneal dialysis solution containing Glucose, Xylitol and L-Carnitine compared to standard PD solutions in Continuous Ambulatory Peritoneal Dialysis (CAPD)

Statistical analysis – Listings

Date: 07/09/2023

Version: final

Author: Antonio Colantoni

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Listing 1.1 - Study IP-001-09 : Disposition of patients

Site no.	Patient no.	Screened	Pat. eligible	Randomized	Treatment no.	Treatment group	Study completed	Treatment completed	Principal Reason for Subject Premature discontinuation
1	01-001	Yes	Yes	Yes	1	B	Yes	Yes	
1	01-002	Yes	Yes	Yes	2	B	Yes	Yes	
1	01-003	Yes	Yes	Yes	3	B	Yes	Yes	
1	01-004	Yes	Yes	Yes	4	A	Yes	Yes	
1	01-005	Yes	Yes	Yes	5	A	Yes	Yes	
1	01-006	Yes	Yes	Yes	6	A	Yes	Yes	
1	01-007	Yes	Yes	Yes	7	A	Yes	Yes	
1	01-008	Yes	Yes	Yes	8	B	Yes	Yes	
1	01-009	Yes	Yes	Yes	9	A	Yes	Yes	
1	01-010	Yes	Yes	Yes	10	A	No	No	Lost to follow up
1	01-011	Yes	Yes	Yes	11	A	Yes	Yes	
5	05-001	Yes	Yes	Yes	1	B	Yes	Yes	
5	05-002	Yes	Yes	Yes	2	B	Yes	Yes	
6	06-001	Yes		No	.	.	No	No	Inclusion/Exclusion criteria not fulfilled
6	06-002	Yes		No	.	.	No	No	Inclusion/Exclusion criteria not fulfilled

Listing 1.2 - Study IP-001-09 : Disposition of patients - Reason for discontinuation - details

Site no.	Patient no.	Principal Reason for Subject Premature discontinuation - details
6	06-001	the patient has been treated with 2.5% glucose solution bags
6	06-002	the patient has been treated with 2.5% glucose solution bags

Listing 1.3 - Study IP-001-09 : Visits dates (dd/mm/yy)

Patient no.	Informed consent	Screening Day -28	Day 0	Day 14	Day 28	Day 42	Day 56	Date of last visit	Date of last treatment
01-001	16/10/2019	16/10/2019	13/11/2019	28/11/2019	12/12/2019	23/12/2019	07/01/2020	07/01/2020	.
01-002	13/11/2019	13/11/2019	11/12/2019	27/12/2019	08/01/2020	22/01/2020	05/02/2020	05/02/2020	.
01-003	13/11/2019	13/11/2019	11/12/2019	27/12/2019	10/01/2020	22/01/2020	05/02/2020	05/02/2020	.
01-004	15/11/2019	15/11/2019	13/12/2019	27/12/2019	09/01/2020	23/01/2020	10/02/2020	10/02/2020	.
01-005	15/11/2019	15/11/2019	13/12/2019	27/12/2019	10/01/2020	24/01/2020	07/02/2020	07/02/2020	.
01-006	20/11/2019	20/11/2019	18/12/2019	03/01/2020	15/01/2020	29/01/2020	12/02/2020	12/02/2020	.
01-007	21/11/2019	21/11/2019	19/12/2019	03/01/2020	16/01/2020	30/01/2020	13/02/2020	13/02/2020	.
01-008	21/11/2019	21/11/2019	19/12/2019	03/01/2020	16/01/2020	30/01/2020	13/02/2020	13/02/2020	.
01-009	26/11/2019	26/11/2019	23/12/2019	07/01/2020	21/01/2020	04/02/2020	18/02/2020	18/02/2020	.
01-010	10/12/2019	10/12/2019	08/01/2020	.	.	.	.	22/01/2020	22/01/2020
01-011	06/02/2020	06/02/2020	05/03/2020	20/03/2020	02/04/2020	16/04/2020	30/04/2020	30/04/2020	.
05-001	13/10/2021	13/10/2021	10/11/2021	26/11/2021	09/12/2021	28/12/2021	22/02/2022	22/02/2022	.
05-002	29/10/2021	29/10/2021	30/11/2021	14/12/2021	30/12/2021	15/01/2022	03/02/2022	03/02/2022	.
06-001	15/12/2021	15/12/2021	.	.	.	.	.	15/12/2021	15/12/2021
06-002	15/12/2021	15/12/2021	.	.	.	.	.	15/12/2021	15/12/2021

Listing 1.4 - Study IP-001-09 : Inclusion criteria

Patient no.	I.C.#1	I.C.#2	I.C.#3	I.C.#4	I.C.#5	I.C.#6	I.C.#7	I.C.#8
01-001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
01-002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
01-003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
01-004	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-005	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-006	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-007	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
01-009	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-010	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
01-011	Yes	Yes	Yes	Yes	Yes	Yes	Na	Na
05-001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
05-002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
06-001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
06-002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Listing 1.5 - Study IP-001-09 : Exclusion criteria

Patient no.	E.C.#1	E.C.#2	E.C.#3	E.C.#4	E.C.#5	E.C.#6	E.C.#7	E.C.#8	E.C.#9	E.C.#10	E.C.#11	E.C.#12
01-001	No	No	No	No	No	No	No	No	Na	No	No	No
01-002	No	No	No	No	No	No	No	No	Na	No	No	No
01-003	No	No	No	No	No	No	No	No	Na	No	No	No
01-004	No	No	No	No	No	No	No	No	Na	No	No	No
01-005	No	No	No	No	No	No	No	No	Na	No	No	No
01-006	No	No	No	No	No	No	No	No	Na	No	No	No
01-007	No	No	No	No	No	No	No	No	Na	No	No	No
01-008	No	No	No	No	No	No	No	No	Na	No	No	No
01-009	No	No	No	No	No	No	No	No	No	No	No	No
01-010	No	No	No	No	No	No	No	No	Na	No	No	No
01-011	No	No	No	No	No	No	No	No	No	No	No	No
05-001	No	No	No	No	No	No	No	No	Na	No	No	No
05-002	No	No	No	No	No	No	No	No	Na	No	No	No
06-001	No	No	No	No	No	No	No	No	Na	No	No	No
06-002	No	No	No	No	No	No	No	No	Na	No	No	No

Listing 2.1 - Study IP-001-09 : Demographic data

Patient no.	Type of patient	Sex	Date of birth (dd/mm/yy)	Age (yrs)	Race	Height (cm)	Weight (kg)	Significant medical/surgery history	Any treatment in the last 3 months	Physical Examination performed?	Physical Examination abnormalities	Pregnancy test (PT) done
01-001	Outpatient patient	Male	19/05/1956	63	White	175	82.0	Yes	Yes	Yes	Yes	
01-002	Outpatient patient	Male	12/01/1957	62	White	186	100.0	Yes	Yes	Yes	No	
01-003	Outpatient patient	Male	02/07/1982	37	White	172	90.5	Yes	Yes	Yes	No	
01-004	Outpatient patient	Female	31/10/1944	75	White	162	66.0	Yes	Yes	Yes	No	Na
01-005	Outpatient patient	Male	22/05/1952	67	White	165	98.0	Yes	Yes	Yes	No	
01-006	Outpatient patient	Male	15/11/1949	70	White	170	80.0	Yes	Yes	Yes	No	
01-007	Outpatient patient	Male	16/03/1959	60	White	175	72.0	Yes	Yes	Yes	No	
01-008	Outpatient patient	Male	09/06/1960	59	White	175	86.0	Yes	Yes	Yes	No	
01-009	Outpatient patient	Female	28/04/1947	72	White	165	93.0	Yes	Yes	Yes	No	Na
01-010	Outpatient patient	Male	13/07/1952	67	White	175	91.0	Yes	Yes	Yes	No	
01-011	Outpatient patient	Female	30/09/1946	73	White	155	51.0	Yes	Yes	Yes	No	Na
05-001	Outpatient patient	Male	04/06/1939	82	White	160	64.2	Yes	Yes	Yes	No	
05-002	Outpatient patient	Male	05/07/1942	79	White	169	66.0	Yes	Yes	Yes	No	
06-001	Outpatient patient	Male	29/04/1935	86	White	168	74.5	Yes	Yes	Yes	No	
06-002	Outpatient patient	Male	29/07/1946	75	White	167	68.7	Yes	Yes	Yes	No	

Listing 2.2 - Study IP-001-09 : Medical and Surgical history (MH)

Patient no.	MH no.	Disease/Surgery	Date of Diagnosis (dd/mm/yy)	Date of Resolution (dd/mm/yy)	Ongoing
01-001	1	Lung tumor	na/07/2018	12/07/2018	No
	2	GERD	na/na/2010		Yes
	3	Tonsillectomy	na/na/1966	na/na/1966	No
	5	Lobectomy	12/07/2018	12/07/2018	No
	6	Peritoneal catheter positioning	na/04/2019	na/04/2019	No
	7	hypertension	na/na/1999		Yes
	8	hypercholesterolemia	na/na/2017		Yes
	9	hyperuricemia	na/na/2017		Yes
01-002	1	Heart attack	na/na/2007	na/na/2007	No
	2	Diabetes mellitus tipe II	na/na/2010		Yes
	3	Chronic lymphatic leukemia	na/na/2013		Yes
	4	Appendectomy	na/na/1975	na/na/1975	No
	5	Left nephrectomy for kidney cancer	na/na/2002	na/na/2002	No
	6	Peritoneal catheter positioning	10/05/2019		Yes
	7	hyperuricemia	na/na/2018		Yes
	8	hypertension	na/na/2010		Yes
	9	hypercholesterolemia	na/na/2015		Yes
01-003	1	Ureteral bladder reflux	na/na/2001		Yes
	2	Pyelonephritis	na/na/2002	na/na/2002	No
	3	Ureteral reimplantation intervention	na/06/2018	na/06/2018	No
	4	Tonsillectomy	na/na/1995	na/na/1995	No
	5	hyperuricemia	na/na/2018		Yes
	6	Benign prostatic hypertrophy	na/na/2005		Yes
	7	Positioning Peritoneal catheter	na/05/2019		Yes
	8	Penicilline and cefalosporine allergy	na/na/na		Yes
	9	Anemia	11/12/2019		Yes
01-004	1	Hypertension	na/na/2000		Yes
	2	Pericarditis	na/na/2005	na/na/2005	No
	3	Parathyroidectomy	na/na/2001	na/na/2001	No
	4	GERD	na/na/2010		Yes
	5	Peritoneal catheter positioning	na/06/2019		Yes
	6	hypercholesterolemia	na/na/2017		Yes
	7	hyperuricemia	na/na/2019		Yes
	8	Appendectomy	na/na/na/	na/na/na	No
	9	Anemia	na/09/2019		Yes

Listing 2.2 - Study IP-001-09 : Medical and Surgical history (MH)

Patient no.	MH no.	Disease/Surgery	Date of Diagnosis (dd/mm/yy)	Date of Resolution (dd/mm/yy)	Ongoing
01-005	1	hypertension	na/na/2002		Yes
	2	hyperuricemia	na/na/2017		Yes
	3	hypercholesterolemia	na/na/2003		Yes
	4	knee prosthesis implant	na/na/2011	na/na/2011	No
	5	peritoneal catheter positioning	na/06/2019		Yes
	6	diabetes mellitus tipe 2	na/na/2005		Yes
	7	cardioaspirin allergy	na/na/na		Yes
	8	Anemia	na/08/2019		Yes
01-006	1	Hypertension	na/na/1980		Yes
	2	Hypothyroidism	na/na/2005		Yes
	3	Peritoneal catheter positioning	na/03/2019		Yes
	4	Left hernioplastic	na/na/2018	na/na/2018	No
	5	Hyperuricemia	na/na/2019		Yes
	6	Anemia	na/na/2019		Yes
01-007	1	Acute myocardial infarction	na/03/2015	na/03/2015	No
	2	Coronary artery angioplasty	na/03/2015	na/03/2015	No
	3	Diabetes mellitus tipe II	na/na/2005	na/na/2012	No
	4	Peritoneal catheter positioning	na/07/2019		Yes
	5	Hypertension	na/na/2015		Yes
	6	Dysplipidemia	na/na/2015		Yes
	7	Hyperuricemia	na/na/2015		Yes
	8	Anxious syndrome	na/na/2010		Yes
	9	allergy to rocefin	na/na/na		Yes
	10	Anemia	na/na/2015		Yes
	12	Chronic Kidney Disease- associated pruritus (CKD- aP)	03/01/2020		Yes
01-008	1	Infarction myocardial	na/na/2005	na/na/2005	No
	2	Coronary angioplasty	na/na/2005	na/na/2005	No
	3	Peritoneal catheter positioning	na/04/2019		Yes
	5	hypertension	na/na/2018		Yes
	6	Anemia	na/na/2019		Yes
	7	Hyperuricemia	na/na/na		Yes
01-009	1	Mild aortic insufficiency	na/na/1980		Yes
	2	Ascending aorta ectasia	na/na/2017		Yes
	3	Hypertension	na/na/1980		Yes
	4	Varicose veins lower limbs	na/na/2000		Yes

Listing 2.2 - Study IP-001-09 : Medical and Surgical history (MH)

Patient no.	MH no.	Disease/Surgery	Date of Diagnosis (dd/mm/yy)	Date of Resolution (dd/mm/yy)	Ongoing
01-009	5	Type B gastritis	na/na/2017		Yes
	6	Hysteroannessiectomy	na/na/2000	na/na/2000	No
	7	Hypothyroidism	na/na/2012		Yes
	8	Appendectomy	na/na/1961	na/na/1961	No
	9	Tonsillectomy	na/na/1963	na/na/1963	No
	10	Umbilical hernia correction	na/na/2015	na/na/2015	No
	11	peritoneal catheter positioning	na/04/2019		Yes
	12	Anemia	na/na/2019		Yes
01-010	1	Aortic insufficiency	na/03/2017		Yes
	3	Hypertension	na/na/2010		Yes
	4	Prostatic hypertrophy	na/na/2017	na/na/2017	No
	5	TURB	na/na/2017	na/na/2017	No
	6	Appendectomy	na/na/1972	na/na/1972	No
	7	Peritoneal catheter positioning	na/07/2019		Yes
	8	Hyperuricemia	na/na/2017		Yes
	9	anemia	na/na/2019		Yes
01-011	1	Hypertension	na/na/2010		Yes
	2	Peritoneal catheter positioning	na/03/2019		Yes
	3	Tonsillectomy	na/na/1954	na/na/1954	No
	4	Radical left mastectomy	na/na/2009	na/na/2009	No
	5	Hyperuricemia	na/na/2017		Yes
	6	anemia	na/na/2019		Yes
05-001	1	Osteoporosis	na/na/na		Yes
	2	Bilateral hip replacement	na/na/2017		Yes
	3	Atrial fibrillation	17/08/2020		Yes
	4	Cholecystectomy	na/na/2000		Yes
	5	Hypertension	na/na/na		Yes
	6	COPD	na/na/na		Yes
	7	prostatic hypertrophy	na/na/na		Yes
	8	Frequent bradycardia	na/na/na		Yes
05-002	1	BPH	na/na/1997	na/na/1998	No
	2	hypertension	na/na/1988		Yes
	3	diabetes mellitus type II	na/na/2000		Yes
	4	dyslipidemia	na/na/2000		Yes
	5	Crohn's disease	na/11/2020		Yes

Listing 2.2 - Study IP-001-09 : Medical and Surgical history (MH)

Patient no.	MH no.	Disease/Surgery	Date of Diagnosis (dd/mm/yy)	Date of Resolution (dd/mm/yy)	Ongoing
05-002	6	Nefroangiosclerosis	07/07/2017		Yes
06-001	1	peritoneal catheter insertion	06/11/2014		Yes
06-002	1	peritoneal catheter insertion	01/01/2016		Yes
	2	kydney transplant	05/11/2019	12/11/2019	No
	3	transplanted kidney explant	22/11/2019	22/11/2019	No
	4	covid relate infection	01/11/2020	15/11/2020	No

Listing 2.3 - Study IP-001-09 : Physical Examination (PE) - abnormalities

Patient no.	PE no.	Test	Result/Description
01-001	1	Other	RIGHT LOWER LIMB EDEMA

Listing 3 - Study IP-001-09 : Clinical parameters

Patient no.	Visit no.	Weight (kg)	Systolic BP (mmHg)	SBP evaluation	Diastolic BP (mmHg)	DBP evaluation	Heart Rate (beats/ min)	HR evaluation	Diuresis (L/day)	Hyperhydratation signs
01-001	Screening	82.0	155	2	95	2	75	2	2.00	No
	Day 0	84.0	140	1	95	2	56	2	2.10	No
	Day 14	82.0	150	2	95	2	53	2	2.00	No
	Day 28	84.0	130	1	80	1	48	2	2.00	No
	Day 42	84.5	155	2	100	2	56	2	2.00	No
	Day 56	83.0	160	2	100	2	56	2	1.80	No
01-002	Screening	100.0	145	2	90	2	65	1	2.50	No
	Day 0	98.0	150	2	80	1	86	1	2.20	No
	Day 14	100.0	145	2	70	1	63	1	2.50	No
	Day 28	98.0	140	1	80	1	82	1	2.50	No
	Day 42	98.0	150	2	70	1	60	1	2.50	No
	Day 56	99.0	155	2	80	1	60	1	2.10	No
01-003	Screening	90.5	130	1	80	1	100	2	1.00	No
	Day 0	88.0	110	1	70	1	90	1	2.10	No
	Day 14	87.0	146	2	80	1	96	1	2.30	No
	Day 28	84.0	105	1	60	1	60	1	1.80	No
	Day 42	88.0	120	1	70	1	85	1	1.80	No
	Day 56	88.0	135	1	70	1	68	1	2.00	No
01-004	Screening	66.0	170	2	80	2	74	1	1.75	No
	Day 0	65.0	145	2	95	2	75	1	1.25	No
	Day 14	65.0	170	2	80	2	79	1	1.50	No
	Day 28	64.0	140	2	90	2	85	1	1.10	No
	Day 42	65.0	150	2	90	2	90	1	1.20	No
	Day 56	64.0	140	2	70	1	96	1	1.10	No
01-005	Screening	98.0	160	2	80	2	63	1	1.50	No
	Day 0	95.0	150	2	80	1	55	2	1.10	No
	Day 14	94.0	130	1	55	2	61	1	1.50	No
	Day 28	90.0	135	1	75	1	70	1	1.50	No
	Day 42	91.0	130	1	60	1	63	1	1.20	No
	Day 56	93.0	140	2	70	1	63	1	1.60	No
01-006	Screening	80.0	125	1	70	1	56	2	2.00	No

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 3 - Study IP-001-09 : Clinical parameters

Patient no.	Visit no.	Weight (kg)	Systolic BP (mmHg)	SBP evaluation	Diastolic BP (mmHg)	DBP evaluation	Heart Rate (beats/ min)	HR evaluation	Diuresis (L/day)	Hyperhydratation signs
01-006	Day 0	78.5	110	1	70	1	50	2	1.60	No
	Day 14	81.0	150	2	90	2	60	1	2.00	No
	Day 28	80.0	150	2	80	1	54	2	1.50	No
	Day 42	81.0	115	1	65	2	64	1	1.75	No
	Day 56	79.5	140	1	85	1	50	2	1.50	No
01-007	Screening	72.0	150	2	90	2	69	1	2.00	No
	Day 0	70.5	165	2	80	1	73	1	2.00	No
	Day 14	73.0	150	2	80	1	65	1	2.00	No
	Day 28	71.5	150	2	90	2	68	1	2.30	No
	Day 42	71.0	130	1	60	1	65	1	1.80	No
	Day 56	71.0	110	1	70	1	72	1	1.75	No
01-008	Screening	86.0	150	2	100	2	70	1	2.00	No
	Day 0	86.0	140	1	80	1	75	1	1.75	No
	Day 14	88.0	128	1	80	1	96	1	1.80	No
	Day 28	87.5	150	2	95	2	85	1	1.80	No
	Day 42	88.0	140	1	80	1	98	1	2.00	No
	Day 56	87.0	110	1	70	1	84	1	1.65	No
01-009	Screening	93.0	150	2	80	1	55	1	2.00	No
	Day 0	97.0	115	1	80	1	67	1	2.70	No
	Day 14	97.0	120	1	70	1	64	1	2.50	No
	Day 28	96.5	105	1	75	1	69	1	2.00	No
	Day 42	95.0	160	2	75	1	65	1	2.50	No
	Day 56	94.5	120	1	75	1	55	2	2.60	No
01-010	Screening	91.0	150	2	70	1	68	1	2.00	No
	Day 0	91.0	160	2	80	1	72	1	2.00	No
	Day 14	.	.	.	.	.	.	.	.	
	Day 28	.	.	.	.	.	.	.	.	
	Day 42	.	.	.	.	.	.	.	.	
	Day 56	.	.	.	.	.	.	.	.	
01-011	Screening	51.0	140	1	80	1	60	1	2.00	No
	Day 0	53.0	120	1	85	2	67	1	1.10	No

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 3 - Study IP-001-09 : Clinical parameters

Patient no.	Visit no.	Weight (kg)	Systolic BP (mmHg)	SBP evaluation	Diastolic BP (mmHg)	DBP evaluation	Heart Rate (beats/ min)	HR evaluation	Diuresis (L/day)	Hyperhydratation signs
01-011	Day 14	50.5	150	2	80	1	51	2	1.20	No
	Day 28	49.0	130	1	70	1	53	2	1.10	No
	Day 42	50.0	150	2	70	1	55	2	1.10	No
	Day 56	51.0	145	2	85	2	70	1	1.40	No
05-001	Screening	64.2	140	1	80	1	70	1	1.40	No
	Day 0	63.4	120	1	80	1	77	1	1.00	No
	Day 14	62.7	130	1	70	1	80	1	1.50	No
	Day 28	62.7	135	1	90	1	85	1	1.60	No
	Day 42	64.5	130	1	90	1	81	1	1.25	No
	Day 56	68.4	150	1	90	1	87	1	1.30	No
05-002	Screening	66.0	140	1	80	1	71	1	0.50	No
	Day 0	67.5	130	1	65	1	75	1	0.55	No
	Day 14	67.0	130	1	70	1	75	1	0.60	No
	Day 28	69.0	135	1	80	1	70	1	0.50	Yes
	Day 42	68.0	140	1	75	1	77	1	0.40	No
	Day 56	68.5	140	1	80	1	70	1	0.50	No
06-001	Screening	74.5	145	1	78	1	67	1	1.10	No
06-002	Screening	68.7	125	1	70	1	59	1	1.60	No

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 4 - Study IP-001-09 : Ulrafiltration, CA 125 and Proteins

Patient no.	Visit no.	1st Daily Bag (mL)	2nd Daily Bag (mL)	3rd Daily Bag (mL)	Nocturnal Bag (mL)	Total ultrafiltration (mL)	CA 125 (U.a./ mL)	Proteins in ultrafiltration (mg/L)
01-001	Screening	-100	-150	0	750	500	23.6	2.2
	Day 0	100	100	0	200	400	54.6	2.2
	Day 14	100	100	0	100	300	62.0	2.2
	Day 28	100	100	0	100	300	145.9	0.8
	Day 42	100	100	0	100	300	.	.
	Day 56	150	100	0	200	450	110.9	0.8
01-002	Screening	100	0	0	400	500	22.8	2.2
	Day 0	150	0	0	250	400	45.5	0.8
	Day 14	150	0	0	250	400	59.8	.
	Day 28	150	0	0	250	400	66.7	0.8
	Day 42	150	0	0	350	500	.	.
	Day 56	150	0	0	250	400	76.8	0.8
01-003	Screening	100	100	0	200	400	60.8	2.2
	Day 0	100	50	0	150	300	.	0.8
	Day 14	50	100	0	150	300	51.8	0.8
	Day 28	50	100	0	150	300	73.7	0.8
	Day 42	50	50	0	200	300	.	.
	Day 56	100	100	0	100	300	104.4	0.8
01-004	Screening	-100	0	0	0	-100	58.3	2.2
	Day 0	0	0	0	0	0	81.0	0.8
	Day 14	100	0	0	0	100	68.0	0.8
	Day 28	200	0	0	0	200	67.9	0.8
	Day 42	200	0	0	0	200	.	.
	Day 56	400	0	0	0	400	52.9	0.8
01-005	Screening	200	0	0	0	200	54.6	2.2
	Day 0	0	0	0	0	0	42.9	0.8
	Day 14	100	0	0	0	100	56.4	0.8
	Day 28	100	0	0	0	100	75.4	0.8
	Day 42	0	0	0	0	0	.	.
	Day 56	0	0	0	0	0	76.4	0.8
01-006	Screening	0	0	0	0	0	29.9	2.2
	Day 0	100	0	0	0	100	52.6	0.8
	Day 14	250	0	0	0	250	45.3	0.8

Listing 4 - Study IP-001-09 : Ulrafiltration, CA 125 and Proteins

Patient no.	Visit no.	1st Daily Bag (mL)	2nd Daily Bag (mL)	3rd Daily Bag (mL)	Nocturnal Bag (mL)	Total ultrafiltration (mL)	CA 125 (U.a./ mL)	Proteins in ultrafiltration (mg/L)
01-006	Day 28	100	0	0	0	100	66.1	0.8
	Day 42	300	0	0	0	300	.	.
	Day 56	300	0	0	0	300	39.5	0.8
01-007	Screening	100	0	0	0	100	106.3	2.2
	Day 0	300	0	0	0	300	184.0	0.8
	Day 14	200	0	0	0	200	203.1	0.8
	Day 28	200	0	0	0	200	209.2	0.8
	Day 42	900	0	0	0	900	.	.
	Day 56	600	0	0	0	600	224.7	0.8
01-008	Screening	50	100	250	0	400	59.4	2.2
	Day 0	50	50	0	200	300	88.6	0.8
	Day 14	150	50	0	100	300	51.9	0.8
	Day 28	50	50	0	200	300	109.4	0.8
	Day 42	200	150	0	250	600	.	.
	Day 56	200	200	0	200	600	90.7	0.8
01-009	Screening	500	0	0	0	500	33.6	2.2
	Day 0	300	0	0	0	300	61.4	0.8
	Day 14	300	0	0	0	300	63.3	0.8
	Day 28	300	0	0	0	300	93.4	0.8
	Day 42	400	0	0	0	400	.	.
	Day 56	500	0	0	0	500	57.7	0.8
01-010	Screening	200	0	0	0	200	38.1	0.8
	Day 0	0	0	0	100	100	35.9	0.8
	Day 14	.	.	.	.	.	.	.
	Day 28	.	.	.	.	.	.	.
	Day 42	.	.	.	.	.	.	.
	Day 56	.	.	.	.	.	.	.
01-011	Screening	100	0	0	0	100	61.4	0.8
	Day 0	250	0	0	0	250	46.2	0.8
	Day 14	300	0	0	0	300	52.3	0.8
	Day 28	300	0	0	0	300	60.9	0.8
	Day 42	250	0	0	0	250	.	.
	Day 56	300	0	0	0	300	41.6	0.8

Listing 4 - Study IP-001-09 : Ulrafiltration, CA 125 and Proteins

Patient no.	Visit no.	1st Daily Bag (mL)	2nd Daily Bag (mL)	3rd Daily Bag (mL)	Nocturnal Bag (mL)	Total ultrafiltration (mL)	CA 125 (U.a./ mL)	Proteins in ultrafiltration (mg/L)
05-001	Screening	-50	-150	0	750	550	.	.
	Day 0	-200	-50	0	650	400	9.9	0.3
	Day 14	100	-100	0	700	700	10.9	0.3
	Day 28	100	-100	0	750	750	11.9	2.6
	Day 42	50	100	200	700	1050	.	.
	Day 56	100	150	50	500	800	10.7	0.3
05-002	Screening	150	150	0	1050	1350	23.2	2.0
	Day 0	100	-100	0	1050	1050	24.0	.
	Day 14	550	50	0	450	1050	25.1	0.0
	Day 28	1050	-1050	0	1000	1000	21.9	0.3
	Day 42	1100	0	300	100	1500	.	.
	Day 56	200	-50	0	1000	1150	22.4	0.2
06-001	Screening	0	0	0	0	0	13.0	20.0
06-002	Screening	0	0	0	0	0	8.1	20.0

Listing 5 - Study IP-001-09 : Uric and Lactic acid

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Uric Acid (UA)	UA unit	UA low	UA high	UA evaluation	Lactic acid (LA)	LA unit	LA low	LA high	LA evaluation
01-001	Screening	2019-10-16	3.3	mg/dl	3.5	8.5	2	.		.	.	.
	Day 0	2019-11-13	3.3	mg/dl	3.5	8.5	2	15.30	mg/dL	10.0	20	1
	Day 14	2019-11-28	7.1	mg/dl	3.5	8.5	1	14.95	mg/dL	10.0	20	1
	Day 28	2019-12-12	7.7	mg/dL	3.5	7.2	2	8.10	mg/dL	10.0	20	2
	Day 42	2019-12-23	7.2	mg/dL	3.5	7.2	1	14.40	mg/dL	10.0	20	1
	Day 56	2020-01-07	6.8	mg/dL	3.5	7.2	1	.	mg/dL	10.0	20	.
01-002	Screening	2018-11-13	4.4		.	.	1	.		.	.	.
	Day 0	2019-12-11	4.2	mg/dL	3.5	7.2	1	11.00	mg/dL	10.0	20	1
	Day 14	2019-12-27	4.7	mg/dL	3.5	7.2	1	14.00	mg/dL	10.0	20	1
	Day 28	2020-01-08	4.3	mg/dL	3.5	7.2	1	17.11	mg/dL	10.0	20	1
	Day 42	2020-01-22	4.4	mg/dL	3.5	7.2	1	10.80	mg/dL	10.0	20	1
	Day 56	2020-02-05	3.9	mg/dL	3.5	7.2	1	17.74	mg/dL	10.0	20	1
01-003	Screening	2019-11-13	5.6	mg/dl	3.5	8.5	1	.		.	.	.
	Day 0	2019-12-11	5.2	mg/dL	3.5	7.2	1	6.00	mg/dL	10.0	20	2
	Day 14	2019-12-27	5.6	mg/dL	3.5	7.2	1	5.00	mg/dL	10.0	20	2
	Day 28	2020-01-10	5.6	mg/dL	3.5	7.2	1	10.80	mg/dL	10.0	20	1
	Day 42	2020-01-22	5.2	mg/dL	3.5	7.2	1	9.00	mg/dL	10.0	20	2
	Day 56	2020-02-05	4.7	mg/dL	3.5	7.2	1	11.00	mg/dL	10.0	20	1
01-004	Screening	2019-11-15	3.7	mg/dl	2.5	6.2	1	.		.	.	.
	Day 0	2019-12-13	4.4	mg/dL	2.6	6.0	1	7.00	mg/dL	10.0	20	2
	Day 14	2019-12-27	4.7	mg/dL	2.6	6.0	1	5.00	mg/dL	10.0	20	2
	Day 28	2020-01-09	4.3	mg/dL	2.6	6.0	1	7.00	mg/dL	10.0	20	2
	Day 42	2020-01-23	4.8	mg/dL	2.6	6.0	1	5.40	mg/dL	10.0	20	2
	Day 56	2020-02-10	5.3	mg/dL	2.6	6.0	1	6.00	mg/dL	10.0	20	2
01-005	Screening	2019-11-15	5.4	mg/dl	3.5	8.5	1	.		.	.	.
	Day 0	2019-12-13	5.9	mg/dL	3.5	7.2	1	11.00	mg/dL	10.0	20	1
	Day 14	2019-12-27	5.9	mg/dL	3.5	7.2	1	8.00	mg/dL	10.0	20	2
	Day 28	2020-01-10	5.9	mg/dL	3.5	7.2	1	12.60	mg/dL	10.0	20	1
	Day 42	2020-01-24	6.1	mg/dL	3.5	7.2	1	19.80	mg/dL	10.0	20	1
	Day 56	2020-02-07	5.9	mg/dL	3.5	7.2	1	16.00	mg/dL	10.0	20	1

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 5 - Study IP-001-09 : Uric and Lactic acid

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Uric Acid (UA)	UA unit	UA low	UA high	UA evaluation	Lactic acid (LA)	LA unit	LA low	LA high	LA evaluation
01-006	Screening	2019-11-20	1.9	mg/dl	3.5	8.5	2	.		.	.	.
	Day 0	2019-12-18	9.9	mg/dL	3.5	7.2	2	9.00	mg/dL	10.0	20	2
	Day 14	2020-01-03	4.8	mg/dL	3.5	7.2	1	15.30	mg/dL	10.0	20	1
	Day 28	2020-01-15	6.9	mg/dL	3.5	7.2	1	7.20	mg/dL	10.0	20	2
	Day 42	2020-01-29	7.5	mg/dL	3.5	7.2	2	13.50	mg/dL	10.0	20	1
	Day 56	2020-02-12	7.3	mg/dL	3.5	7.2	2	8.00	mg/dL	10.0	20	2
01-007	Screening	2019-11-21	4.5	mg/dl	3.5	8.5	1	.		.	.	.
	Day 0	2019-12-19	4.3	mg/dL	3.5	7.2	1	10.00	mg/dL	10.0	20	1
	Day 14	2020-01-03	4.2	mg/dL	3.5	7.2	1	9.90	mg/dL	10.0	20	2
	Day 28	2020-01-16	4.6	mg/dL	3.5	7.2	1	11.00	mg/dL	10.0	20	1
	Day 42	2020-01-30	5.1	mg/dL	3.5	7.2	1	13.00	mg/dL	10.0	20	1
	Day 56	2020-02-13	5.2	mg/dL	3.5	7.2	1	8.00	mg/dL	10.0	20	2
01-008	Screening	2019-11-21	8.9	mg/dl	3.5	8.5	2	.		.	.	.
	Day 0	2019-12-19	.	mg/dL	3.5	7.2	.	6.00	mg/dL	10.0	20	2
	Day 14	2020-01-03	9.7	mg/dL	3.5	7.2	2	9.90	mg/dL	10.0	20	2
	Day 28	2020-01-16	7.6	mg/dL	3.5	7.2	2	9.00	mg/dL	10.0	20	2
	Day 42	2020-01-30	5.9	mg/dL	3.5	7.2	1	8.00	mg/dL	10.0	20	2
	Day 56	2020-02-13	5.9	mg/dL	3.5	7.2	1	6.00	mg/dL	10.0	20	2
01-009	Screening	2019-11-26	6.6	mg/dl	2.5	6.2	2	.		.	.	.
	Day 0	2019-12-23	6.3	mg/dL	2.6	6.0	2	7.20	mg/dL	10.0	20	2
	Day 14	2020-01-07	7.5	mg/dL	2.6	6.0	2	.	mg/dL	10.0	20	.
	Day 28	2020-01-21	6.7	mg/dL	2.6	6.0	2	10.00	mg/dL	10.0	20	1
	Day 42	2020-02-04	7.3	mg/dL	2.6	6.0	2	6.00	mg/dL	10.0	20	2
	Day 56	2020-02-18	6.2	mg/dL	2.6	6.0	2	9.90	mg/dL	10.0	20	2
01-010	Screening	2019-12-10	4.8	mg/dL	3.5	7.2	1	.		.	.	.
	Day 0	2020-01-08	4.8	mg/dL	3.5	7.2	1	8.10	mg/dL	10.0	20	2
	Day 14		.		.	.	.	.		.	.	.
	Day 28		.		.	.	.	.		.	.	.
	Day 42		.		.	.	.	.		.	.	.
	Day 56		.		.	.	.	.		.	.	.

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 5 - Study IP-001-09 : Uric and Lactic acid

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Uric Acid (UA)	UA unit	UA low	UA high	UA evaluation	Lactic acid (LA)	LA unit	LA low	LA high	LA evaluation
01-011	Screening	2020-02-06	3.3	mg/dL	2.6	6.0	1	.		.	.	.
	Day 0	2020-03-05	4.5	mg/dL	2.6	6.0	1	21.00	mg/dL	10.0	20	2
	Day 14	2020-03-20	4.3	mg/dL	2.6	6.0	1	19.80	mg/dL	10.0	20	1
	Day 28	2020-04-02	4.1	mg/dL	2.6	6.0	1	13.50	mg/dL	10.0	20	1
	Day 42	2020-04-16	5.0	mg/dL	2.6	6.0	1	.	mg/dL	10.0	20	.
	Day 56	2020-04-30	5.3	mg/dL	2.6	6.0	1	20.00	mg/dL	10.0	20	1
05-001	Screening	2021-10-13	4.0	mg/dL	3.5	7.2	1	.		.	.	.
	Day 0	2021-11-10	4.9	mg/dL	3.5	7.2	1	0.70	mmol/L	0.4	2	1
	Day 14	2021-11-26	3.7	mg/dL	3.5	7.2	1	0.90	mmol/L	0.4	2	1
	Day 28	2021-12-09	3.5	mg/dL	3.5	7.2	1	.	mmol/L	0.4	2	.
	Day 42	2021-12-28	4.5	mg/dL	3.5	7.2	1	1.10	mmol/L	0.4	2	1
	Day 56	2022-02-22	4.0	mg/dL	3.5	7.2	1	1.40	mmol/L	0.4	2	1
05-002	Screening	2021-10-29	5.0	mg/dL	3.5	7.2	1	.		.	.	.
	Day 0	2021-11-30	4.4	mg/dL	3.5	7.2	1	0.80	mmol/L	0.4	2	1
	Day 14	2021-12-14	2.7	mg/dL	3.5	7.2	2	1.10	mmol/L	0.4	2	1
	Day 28	2021-12-30	5.1	mg/dL	3.5	7.2	1	0.60	mmol/L	0.4	2	1
	Day 42	2022-01-15	4.9	mg/dL	3.5	7.2	1	0.60	mmol/L	0.4	2	1
	Day 56	2022-02-03	5.1	mg/dL	3.5	7.2	1	0.80	mmol/L	0.4	2	1
06-001	Screening	2021-12-15	3.4	mg/dL	3.5	7.0	2	.		.	.	.
06-002	Screening	2021-12-15	6.4	mg/dL	3.5	7.0	1	.		.	.	.

Evaluation: 1=Normal; 2=Not Clinically Significant; 3=Clinically sign. for concomitant disease; 4=Clinically sign. for the pathology under study

Listing 6.1 - Study IP-001-09 : Haematology - RBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	3.90	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	3.77	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	3.84	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	3.43	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	3.59	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	3.48	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-002	Screening	2018-11-13	Yes	4.15	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	4.17	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	4.06	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	4.28	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	4.09	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	4.17	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	3.34	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	3.03	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	3.03	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	2.92	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	3.20	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	3.44	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	3.42	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	3.46	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	3.51	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	3.51	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	3.41	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	3.36	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	3.27	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	3.07	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	3.22	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	3.73	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	3.91	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	3.89	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	3.80	10^6/mmc	4.50	5.30	.	Not Clinically Significant

Listing 6.1 - Study IP-001-09 : Haematology - RBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	3.92	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	4.13	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	4.15	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	4.22	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	4.26	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-007	Screening	2019-11-21	Yes	4.38	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	4.21	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	3.72	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	3.62	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	3.35	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	2.95	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	4.05	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	3.91	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	4.03	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	3.75	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	3.71	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	3.53	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	3.44	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2019-12-23	Yes	3.50	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	3.70	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	3.66	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	3.88	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	3.84	10^6/mmc	4.50	5.30	.	Not Clinically Significant
01-010	Screening	2019-12-10	Yes	3.40	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	3.71	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	4.26	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 0	2020-03-05	Yes	4.48	10^6/mmc	4.50	5.30	.	Not Clinically Significant

Listing 6.1 - Study IP-001-09 : Haematology - RBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	4.12	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	3.97	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	3.65	10^6/mmc	4.50	5.30	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	3.68	10^6/mmc	4.50	5.30	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	4.30	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	4.07	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	3.93	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	3.30	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 42	2021-12-28	Yes	3.44	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	3.89	10^6/uL	4.54	5.78	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	3.84	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	4.31	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	4.64	10^6/uL	4.54	5.78	.	Normal
	Day 28	2021-12-30	Yes	4.18	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	4.41	10^6/uL	4.54	5.78	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	4.06	10^6/uL	4.54	5.78	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	3.31	10^12/L	4.50	5.50	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	3.67	10^12/L	4.50	5.50	.	Not Clinically Significant

Listing 6.2 - Study IP-001-09 : Haematology - Hematocrit

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	36.0	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	35.8	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	36.0	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	31.8	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	33.7	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	32.6	%	37.0	49.0	.	Not Clinically Significant
01-002	Screening	2018-11-13	Yes	38.0	%	37.0	49.0	.	Normal
	Day 0	2019-12-11	Yes	38.1	%	37.0	49.0	.	Normal
	Day 14	2019-12-27	Yes	36.8	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	39.5	%	37.0	49.0	.	Normal
	Day 42	2020-01-22	Yes	37.9	%	37.0	49.0	.	Normal
	Day 56	2020-02-05	Yes	38.8	%	37.0	49.0	.	Normal
01-003	Screening	2019-11-13	Yes	29.2	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	26.9	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	26.5	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	25.8	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	28.7	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	31.4	%	37.0	49.0	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	33.1	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	33.8	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	34.0	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	33.5	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	33.0	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	32.5	%	37.0	49.0	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	29.5	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	27.6	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	29.6	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	33.5	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	35.3	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	34.4	%	37.0	49.0	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	34.6	%	37.0	49.0	.	Not Clinically Significant

Listing 6.2 - Study IP-001-09 : Haematology - Hematocrit

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	35.1	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	37.0	%	37.0	49.0	.	Normal
	Day 28	2020-01-15	Yes	36.9	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	38.1	%	37.0	49.0	.	Normal
	Day 56	2020-02-12	Yes	37.6	%	37.0	49.0	.	Normal
01-007	Screening	2019-11-21	Yes	37.1	%	37.0	49.0	.	Normal
	Day 0	2019-12-19	Yes	35.6	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	32.5	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	30.8	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	28.7	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	25.8	%	37.0	49.0	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	36.9	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	35.6	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	36.4	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	33.9	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	34.0	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	32.4	%	37.0	49.0	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	31.6	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2019-12-23	Yes	31.9	%	37.0	49.0	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	33.0	%	37.0	49.0	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	33.8	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	11.8	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	34.9	%	37.0	49.0	.	Not Clinically Significant
01-010	Screening	2019-12-10	Yes	33.0	%	37.0	49.0	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	36.0	%	37.0	49.0	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	40.2	%	37.0	49.0	.	Normal
	Day 0	2020-03-05	Yes	42.0	%	37.0	49.0	.	Normal

Listing 6.2 - Study IP-001-09 : Haematology - Hematocrit

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	37.4	%	37.0	49.0	.	Normal
	Day 28	2020-04-02	Yes	35.3	%	37.0	49.0	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	32.6	%	37.0	49.0	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	33.3	%	37.0	49.0	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	39.9	%	38.9	50.9	.	Normal
	Day 0	2021-11-10	Yes	35.9	%	38.9	50.9	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	36.5	%	38.9	50.9	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	29.2	%	38.9	50.9	.	Not Clinically Significant
	Day 42	2021-12-28	Yes	31.5	%	38.9	50.9	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	35.1	%	38.9	50.9	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	35.4	%	38.9	50.9	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	39.1	%	38.9	50.9	.	Normal
	Day 14	2021-12-14	Yes	40.2	%	38.9	50.9	.	Normal
	Day 28	2021-12-30	Yes	35.8	%	38.9	50.9	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	36.1	%	38.9	50.9	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	33.4	%	38.9	50.9	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	31.2	%	40.0	50.0	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	35.1	%	40.0	50.0	.	Not Clinically Significant

Listing 6.3 - Study IP-001-09 : Haematology - Hemoglobin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	11.9	g/dl	13.0	16.0	.	Clinically significant for concomitant disease
	Day 0	2019-11-13	Yes	11.3	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	11.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	10.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	10.9	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	10.6	g/dl	13.0	16.0	.	Not Clinically Significant
01-002	Screening	2018-11-13	Yes	12.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	11.8	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	11.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	12.3	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	11.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	11.9	g/dl	13.0	16.0	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	9.9	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	8.9	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	8.8	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	8.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	9.3	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	10.1	g/dl	13.0	16.0	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	10.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	10.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	10.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	10.8	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	10.4	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	10.2	g/dl	13.0	16.0	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	9.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	8.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	9.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	10.4	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	11.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	10.7	g/dl	13.0	16.0	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	11.3	g/dl	13.0	16.0	.	Not Clinically Significant

Listing 6.3 - Study IP-001-09 : Haematology - Hemoglobin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	11.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	12.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	12.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	12.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	12.3	g/dl	13.0	16.0	.	Not Clinically Significant
01-007	Screening	2019-11-21	Yes	12.4	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	11.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	10.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	10.1	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	9.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	8.2	g/dl	13.0	16.0	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	11.8	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	11.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	12.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	11.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	11.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	10.5	g/dl	13.0	16.0	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	10.3	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 0	2019-12-23	Yes	10.5	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	11.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	11.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	35.0	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	11.4	g/dl	13.0	16.0	.	Not Clinically Significant
01-010	Screening	2019-12-10	Yes	10.1	g/dl	13.0	16.0	.	Clinically sign. for the pathology under study
	Day 0	2020-01-08	Yes	11.3	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	12.6	g/dl	13.0	16.0	.	Clinically sign. for the pathology under study
	Day 0	2020-03-05	Yes	13.2	g/dl	13.0	16.0	.	Normal

Listing 6.3 - Study IP-001-09 : Haematology - Hemoglobin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	12.2	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	11.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	10.6	g/dl	13.0	16.0	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	10.9	g/dl	13.0	16.0	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	12.2	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	11.6	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	11.2	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	9.4	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 42	2021-12-28	Yes	10.4	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	11.5	gr/dl	13.3	17.2	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	11.2	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	12.2	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	12.7	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	11.9	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	11.8	gr/dl	13.3	17.2	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	11.2	gr/dl	13.3	17.2	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	10.6	g/dL	13.0	17.0	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	12.0	g/dL	13.0	17.0	.	Not Clinically Significant

Listing 6.4 - Study IP-001-09 : Haematology - WBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	6.88	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-11-13	Yes	8.30	10^3/uL	4.0	10.0	.	Normal
	Day 14	2019-11-28	Yes	8.01	10^3/uL	4.0	10.0	.	Normal
	Day 28	2019-12-12	Yes	7.83	10^3/uL	4.0	10.0	.	Normal
	Day 42	2019-12-23	Yes	6.52	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-01-07	Yes	7.20	10^3/uL	4.0	10.0	.	Normal
01-002	Screening	2018-11-13	Yes	32.86	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	31.21	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	35.84	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	35.75	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	33.75	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	29.90	10^3/uL	4.0	10.0	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	8.17	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-12-11	Yes	8.15	10^3/uL	4.0	10.0	.	Normal
	Day 14	2019-12-27	Yes	6.17	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-10	Yes	9.45	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-01-22	Yes	6.04	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-05	Yes	6.97	10^3/uL	4.0	10.0	.	Normal
01-004	Screening	2019-11-15	Yes	6.69	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-12-13	Yes	9.13	10^3/uL	4.0	10.0	.	Normal
	Day 14	2019-12-27	Yes	7.78	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-09	Yes	8.03	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-01-23	Yes	8.09	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-10	Yes	7.59	10^3/uL	4.0	10.0	.	Normal
01-005	Screening	2019-11-15	Yes	7.86	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-12-13	Yes	6.01	10^3/uL	4.0	10.0	.	Normal
	Day 14	2019-12-27	Yes	4.75	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-10	Yes	5.23	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-01-24	Yes	5.98	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-07	Yes	6.01	10^3/uL	4.0	10.0	.	Normal
01-006	Screening	2019-11-20	Yes	6.29	10^3/uL	4.0	10.0	.	Normal

Listing 6.4 - Study IP-001-09 : Haematology - WBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	5.87	10^3/uL	4.0	10.0	.	Normal
	Day 14	2020-01-03	Yes	5.76	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-15	Yes	6.04	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-01-29	Yes	5.01	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-12	Yes	7.00	10^3/uL	4.0	10.0	.	Normal
01-007	Screening	2019-11-21	Yes	11.37	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	14.27	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	10.12	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	10.61	10^3/uL	4.0	10.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	9.11	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-13	Yes	6.45	10^3/uL	4.0	10.0	.	Normal
01-008	Screening	2019-11-21	Yes	7.63	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-12-19	Yes	6.05	10^3/uL	4.0	10.0	.	Normal
	Day 14	2020-01-03	Yes	8.24	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-16	Yes	6.49	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-01-30	Yes	6.40	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-13	Yes	7.31	10^3/uL	4.0	10.0	.	Normal
01-009	Screening	2019-11-26	Yes	4.82	10^3/uL	4.0	10.0	.	Normal
	Day 0	2019-12-23	Yes	4.68	10^3/uL	4.0	10.0	.	Normal
	Day 14	2020-01-07	Yes	4.58	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-01-21	Yes	4.90	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-02-04	Yes	4.27	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-02-18	Yes	5.18	10^3/uL	4.0	10.0	.	Normal
01-010	Screening	2019-12-10	Yes	4.59	10^3/uL	4.0	10.0	.	Normal
	Day 0	2020-01-08	Yes	4.28	10^3/uL	4.0	10.0	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	7.79	10^3/uL	4.0	10.0	.	Normal
	Day 0	2020-03-05	Yes	6.52	10^3/uL	4.0	10.0	.	Normal

Listing 6.4 - Study IP-001-09 : Haematology - WBC count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	8.32	10^3/uL	4.0	10.0	.	Normal
	Day 28	2020-04-02	Yes	8.29	10^3/uL	4.0	10.0	.	Normal
	Day 42	2020-04-16	Yes	8.88	10^3/uL	4.0	10.0	.	Normal
	Day 56	2020-04-30	Yes	7.99	10^3/uL	4.0	10.0	.	Normal
05-001	Screening	2021-10-13	No	5.45	10^3/uL	3.7	9.7	.	Normal
	Day 0	2021-11-10	Yes	4.19	10^3/uL	3.7	9.7	.	Normal
	Day 14	2021-11-26	Yes	5.97	10^3/uL	3.7	9.7	.	Normal
	Day 28	2021-12-09	Yes	5.27	10^3/uL	3.7	9.7	.	Normal
	Day 42	2021-12-28	Yes	4.75	10^3/uL	3.7	9.7	.	Normal
	Day 56	2022-02-22	Yes	5.81	10^3/uL	3.7	9.7	.	Normal
05-002	Screening	2021-10-29	Yes	9.53	10^3/uL	3.7	9.7	.	Normal
	Day 0	2021-11-30	Yes	11.04	10^3/uL	3.7	9.7	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	8.88	10^3/uL	3.7	9.7	.	Normal
	Day 28	2021-12-30	Yes	6.73	10^3/uL	3.7	9.7	.	Normal
	Day 42	2022-01-15	Yes	9.18	10^3/uL	3.7	9.7	.	Normal
	Day 56	2022-02-03	Yes	7.66	10^3/uL	3.7	9.7	.	Normal
06-001	Screening	2021-12-15	Yes	6.94	10^9/L	4.0	10.0	.	Normal
06-002	Screening	2021-12-15	Yes	5.83	10^9/L	4.0	10.0	.	Not Clinically Significant

Listing 6.5 - Study IP-001-09 : Haematology - Neutrophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	3.82	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-11-13	Yes	5.05	10^3/uL	2.1	7.1	.	Normal
	Day 14	2019-11-28	Yes	4.39	10^3/uL	2.1	7.1	.	Normal
	Day 28	2019-12-12	Yes	4.96	10^3/uL	2.1	7.1	.	Normal
	Day 42	2019-12-23	Yes	3.47	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-01-07	Yes	4.32	10^3/uL	2.1	7.1	.	Normal
01-002	Screening	2018-11-13	Yes	3.89	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-11	Yes	3.57	10^3/uL	2.1	7.1	.	Normal
	Day 14	2019-12-27	Yes	4.07	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-08	Yes	7.75	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	5.19	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-05	Yes	3.26	10^3/uL	2.1	7.1	.	Normal
01-003	Screening	2019-11-13	Yes	6.14	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-11	Yes	5.88	10^3/uL	2.1	7.1	.	Normal
	Day 14	2019-12-27	Yes	4.37	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-10	Yes	7.77	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	4.33	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-05	Yes	4.98	10^3/uL	2.1	7.1	.	Normal
01-004	Screening	2019-11-15	Yes	4.72	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-13	Yes	6.72	10^3/uL	2.1	7.1	.	Normal
	Day 14	2019-12-27	Yes	6.09	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-09	Yes	5.96	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-01-23	Yes	6.09	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-10	Yes	5.66	10^3/uL	2.1	7.1	.	Normal
01-005	Screening	2019-11-15	Yes	6.05	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-13	Yes	4.42	10^3/uL	2.1	7.1	.	Normal
	Day 14	2019-12-27	Yes	3.48	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-10	Yes	3.62	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-01-24	Yes	4.21	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-07	Yes	4.07	10^3/uL	2.1	7.1	.	Normal
01-006	Screening	2019-11-20	Yes	3.85	10^3/uL	2.1	7.1	.	Normal

Listing 6.5 - Study IP-001-09 : Haematology - Neutrophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	3.67	10^3/uL	2.1	7.1	.	Normal
	Day 14	2020-01-03	Yes	3.50	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-15	Yes	3.84	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-01-29	Yes	2.80	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-12	Yes	4.78	10^3/uL	2.1	7.1	.	Normal
01-007	Screening	2019-11-21	Yes	9.24	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	11.35	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	7.63	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	8.11	10^3/uL	2.1	7.1	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	6.52	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-13	Yes	3.82	10^3/uL	2.1	7.1	.	Normal
01-008	Screening	2019-11-21	Yes	4.88	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-19	Yes	4.03	10^3/uL	2.1	7.1	.	Normal
	Day 14	2020-01-03	Yes	4.84	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-16	Yes	4.11	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-01-30	Yes	3.81	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-13	Yes	4.68	10^3/uL	2.1	7.1	.	Normal
01-009	Screening	2019-11-26	Yes	2.56	10^3/uL	2.1	7.1	.	Normal
	Day 0	2019-12-23	Yes	2.52	10^3/uL	2.1	7.1	.	Normal
	Day 14	2020-01-07	Yes	2.72	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-01-21	Yes	2.93	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-02-04	Yes	2.50	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-02-18	Yes	3.02	10^3/uL	2.1	7.1	.	Normal
01-010	Screening	2019-12-10	Yes	3.19	10^3/uL	2.1	7.1	.	Normal
	Day 0	2020-01-08	Yes	3.02	10^3/uL	2.1	7.1	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	5.10	10^3/uL	2.1	7.1	.	Normal
	Day 0	2020-03-05	Yes	4.45	10^3/uL	2.1	7.1	.	Normal

Listing 6.5 - Study IP-001-09 : Haematology - Neutrophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	5.86	10^3/uL	2.1	7.1	.	Normal
	Day 28	2020-04-02	Yes	6.19	10^3/uL	2.1	7.1	.	Normal
	Day 42	2020-04-16	Yes	5.98	10^3/uL	2.1	7.1	.	Normal
	Day 56	2020-04-30	Yes	5.54	10^3/uL	2.1	7.1	.	Normal
05-001	Screening	2021-10-13	No	58.90	%	42.9	78.4	.	Normal
	Day 0	2021-11-10	Yes	50.00	%	42.9	78.4	.	Normal
	Day 14	2021-11-26	Yes	62.20	%	42.9	78.4	.	Normal
	Day 28	2021-12-09	Yes	61.20	%	42.9	78.4	.	Normal
	Day 42	2021-12-28	Yes	55.20	%	42.9	78.4	.	Normal
	Day 56	2022-02-22	Yes	67.30	%	42.9	78.4	.	Normal
05-002	Screening	2021-10-29	Yes	81.70	%	42.9	78.4	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	78.50	%	42.9	78.4	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	70.80	%	42.9	78.4	.	Normal
	Day 28	2021-12-30	Yes	73.70	%	42.9	78.4	.	Normal
	Day 42	2022-01-15	Yes	74.40	%	42.9	78.4	.	Normal
	Day 56	2022-02-03	Yes	70.70	%	42.9	78.4	.	Normal
06-001	Screening	2021-12-15	Yes	70.90	%	40.0	80.0	.	Normal
06-002	Screening	2021-12-15	Yes	64.00	%	40.0	80.0	.	Not Clinically Significant

Listing 6.6 - Study IP-001-09 : Haematology - Basophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	0.01	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-11-13	Yes	0.01	10^3/uL	0.0	0.2	.	Normal
	Day 14	2019-11-28	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 28	2019-12-12	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 42	2019-12-23	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-01-07	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
01-002	Screening	2018-11-13	Yes	0.11	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-12-11	Yes	0.09	10^3/uL	0.0	0.2	.	Normal
	Day 14	2019-12-27	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-08	Yes	0.09	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-01-22	Yes	0.11	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-05	Yes	0.09	10^3/uL	0.0	0.2	.	Normal
01-003	Screening	2019-11-13	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-12-11	Yes	0.04	10^3/uL	0.0	0.2	.	Normal
	Day 14	2019-12-27	Yes	0.01	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-10	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-01-22	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-05	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
01-004	Screening	2019-11-15	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-12-13	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 14	2019-12-27	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-09	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-01-23	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-10	Yes	0.04	10^3/uL	0.0	0.2	.	Normal
01-005	Screening	2019-11-15	Yes	0.08	10^3/uL	0.0	0.2	.	Normal
	Day 0	2019-12-13	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
	Day 14	2019-12-27	Yes	0.03	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-01-10	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-01-24	Yes	0.07	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-02-07	Yes	0.06	10^3/uL	0.0	0.2	.	Normal
01-006	Screening	2019-11-20	Yes	0.06	10^3/uL	0.0	0.2	.	Normal

Listing 6.6 - Study IP-001-09 : Haematology - Basophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	0.04	10^3/uL	0.0	0.2	.	Normal	
	Day 14	2020-01-03	Yes	0.06	10^3/uL	0.0	0.2	.	Normal	
	Day 28	2020-01-15	Yes	0.06	10^3/uL	0.0	0.2	.	Normal	
	Day 42	2020-01-29	Yes	0.06	10^3/uL	0.0	0.2	.	Normal	
	Day 56	2020-02-12	Yes	0.07	10^3/uL	0.0	0.2	.	Normal	
01-007	Screening	2019-11-21	Yes	0.06	10^3/uL	0.0	0.2	.	Normal	
	Day 0	2019-12-19	Yes	0.06	10^3/uL	0.0	0.2	.	Normal	
	Day 14	2020-01-03	Yes	0.06	10^3/uL	0.0	0.2	.	Normal	
	Day 28	2020-01-16	Yes	0.06	10^3/uL	0.0	0.2	.	Normal	
	Day 42	2020-01-30	Yes	0.06	10^3/uL	0.0	0.2	.	Normal	
	Day 56	2020-02-13	Yes	0.03	10^3/uL	0.0	0.2	.	Normal	
01-008	Screening	2019-11-21	Yes	0.09	10^3/uL	0.0	0.2	.	Normal	
	Day 0	2019-12-19	Yes	0.07	10^3/uL	0.0	0.2	.	Normal	
	Day 14	2020-01-03	Yes	0.10	10^3/uL	0.0	0.2	.	Normal	
	Day 28	2020-01-16	Yes	0.10	10^3/uL	0.0	0.2	.	Normal	
	Day 42	2020-01-30	Yes	0.09	10^3/uL	0.0	0.2	.	Normal	
	Day 56	2020-02-13	Yes	0.08	10^3/uL	0.0	0.2	.	Normal	
01-009	Screening	2019-11-26	Yes	0.05	10^3/uL	0.0	0.2	.	Normal	
	Day 0	2019-12-23	Yes	0.04	10^3/uL	0.0	0.2	.	Normal	
	Day 14	2020-01-07	Yes	0.05	10^3/uL	0.0	0.2	.	Normal	
	Day 28	2020-01-21	Yes	0.03	10^3/uL	0.0	0.2	.	Normal	
	Day 42	2020-02-04	Yes	0.04	10^3/uL	0.0	0.2	.	Normal	
	Day 56	2020-02-18	Yes	0.04	10^3/uL	0.0	0.2	.	Normal	
01-010	Screening	2019-12-10	Yes	0.02	10^3/uL	0.0	0.2	.	Normal	
	Day 0	2020-01-08	Yes	0.01	10^3/uL	0.0	0.2	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	0.04	10^3/uL	0.0	0.2	.	Normal	
	Day 0	2020-03-05	Yes	0.04	10^3/uL	0.0	0.2	.	Normal	

Listing 6.6 - Study IP-001-09 : Haematology - Basophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	0.03	10^3/uL	0.0	0.2	.	Normal
	Day 28	2020-04-02	Yes	0.02	10^3/uL	0.0	0.2	.	Normal
	Day 42	2020-04-16	Yes	0.05	10^3/uL	0.0	0.2	.	Normal
	Day 56	2020-04-30	Yes	0.05	10^3/uL	0.0	0.2	.	Normal
05-001	Screening	2021-10-13	No	0.40	%	0.3	1.3	.	Normal
	Day 0	2021-11-10	Yes	0.50	%	0.3	1.3	.	Normal
	Day 14	2021-11-26	Yes	0.50	%	0.3	1.3	.	Normal
	Day 28	2021-12-09	Yes	0.30	%	0.3	1.3	.	Normal
	Day 42	2021-12-28	Yes	1.20	%	0.3	1.3	.	Normal
	Day 56	2022-02-22	Yes	0.50	%	0.3	1.3	.	Normal
05-002	Screening	2021-10-29	Yes	0.50	%	0.3	1.3	.	Normal
	Day 0	2021-11-30	Yes	0.40	%	0.3	1.3	.	Normal
	Day 14	2021-12-14	Yes	0.70	%	0.3	1.3	.	Normal
	Day 28	2021-12-30	Yes	0.90	%	0.3	1.3	.	Normal
	Day 42	2022-01-15	Yes	1.20	%	0.3	1.3	.	Normal
	Day 56	2022-02-03	Yes	0.60	%	0.3	1.3	.	Normal
06-001	Screening	2021-12-15	Yes	0.20	%	0.0	1.2	.	Normal
06-002	Screening	2021-12-15	Yes	0.40	%	0.0	1.2	.	Not Clinically Significant

Listing 6.7 - Study IP-001-09 : Haematology - Eosinophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	0.14	10^3/uL	0.0	0.5	.	Normal
	Day 0	2019-11-13	Yes	0.19	10^3/uL	0.0	0.5	.	Normal
	Day 14	2019-11-28	Yes	0.21	10^3/uL	0.0	0.5	.	Normal
	Day 28	2019-12-12	Yes	0.22	10^3/uL	0.0	0.5	.	Normal
	Day 42	2019-12-23	Yes	0.13	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-01-07	Yes	0.20	10^3/uL	0.0	0.5	.	Normal
01-002	Screening	2018-11-13	Yes	0.30	10^3/uL	0.0	0.5	.	Normal
	Day 0	2019-12-11	Yes	0.31	10^3/uL	0.0	0.5	.	Normal
	Day 14	2019-12-27	Yes	0.24	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-08	Yes	0.23	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-01-22	Yes	0.23	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-05	Yes	0.24	10^3/uL	0.0	0.5	.	Normal
01-003	Screening	2019-11-13	Yes	0.00	10^3/uL	0.0	0.5	.	Normal
	Day 0	2019-12-11	Yes	0.00	10^3/uL	0.0	0.5	.	Normal
	Day 14	2019-12-27	Yes	0.00	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-10	Yes	0.00	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-01-22	Yes	0.00	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-05	Yes	0.00	10^3/uL	0.0	0.5	.	Normal
01-004	Screening	2019-11-15	Yes	0.27	10^3/uL	0.0	0.5	.	Normal
	Day 0	2019-12-13	Yes	0.35	10^3/uL	0.0	0.5	.	Normal
	Day 14	2019-12-27	Yes	0.20	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-09	Yes	0.29	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-01-23	Yes	0.26	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-10	Yes	0.26	10^3/uL	0.0	0.5	.	Normal
01-005	Screening	2019-11-15	Yes	0.13	10^3/uL	0.0	0.5	.	Normal
	Day 0	2019-12-13	Yes	0.14	10^3/uL	0.0	0.5	.	Normal
	Day 14	2019-12-27	Yes	0.10	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-10	Yes	0.09	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-01-24	Yes	0.08	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-07	Yes	0.12	10^3/uL	0.0	0.5	.	Normal
01-006	Screening	2019-11-20	Yes	0.26	10^3/uL	0.0	0.5	.	Normal

Listing 6.7 - Study IP-001-09 : Haematology - Eosinophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	0.24	10^3/uL	0.0	0.5	.	Normal
	Day 14	2020-01-03	Yes	0.25	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-15	Yes	0.27	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-01-29	Yes	0.37	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-12	Yes	0.27	10^3/uL	0.0	0.5	.	Normal
01-007	Screening	2019-11-21	Yes	0.31	10^3/uL	0.0	0.5	.	Normal
	Day 0	2019-12-19	Yes	0.65	10^3/uL	0.0	0.5	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	0.43	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-16	Yes	0.48	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-01-30	Yes	0.45	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-13	Yes	0.26	10^3/uL	0.0	0.5	.	Normal
01-008	Screening	2019-11-21	Yes	0.46	10^3/uL	0.0	0.5	.	Normal
	Day 0	2019-12-19	Yes	0.18	10^3/uL	0.0	0.5	.	Normal
	Day 14	2020-01-03	Yes	0.34	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-16	Yes	0.30	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-01-30	Yes	0.26	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-13	Yes	0.25	10^3/uL	0.0	0.5	.	Normal
01-009	Screening	2019-11-26	Yes	0.24	10^3/uL	0.0	0.5	.	Normal
	Day 0	2019-12-23	Yes	0.17	10^3/uL	0.0	0.5	.	Normal
	Day 14	2020-01-07	Yes	0.12	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-01-21	Yes	0.17	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-02-04	Yes	0.13	10^3/uL	0.0	0.5	.	Normal
	Day 56	2020-02-18	Yes	0.19	10^3/uL	0.0	0.5	.	Normal
01-010	Screening	2019-12-10	Yes	0.25	10^3/uL	0.0	0.5	.	Normal
	Day 0	2020-01-08	Yes	0.26	10^3/uL	0.0	0.5	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	0.53	10^3/uL	0.0	0.5	.	Not Clinically Significant
	Day 0	2020-03-05	Yes	0.51	10^3/uL	0.0	0.5	.	Not Clinically Significant

Listing 6.7 - Study IP-001-09 : Haematology - Eosinophils

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	0.37	10^3/uL	0.0	0.5	.	Normal
	Day 28	2020-04-02	Yes	0.22	10^3/uL	0.0	0.5	.	Normal
	Day 42	2020-04-16	Yes	0.66	10^3/uL	0.0	0.5	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	0.58	10^3/uL	0.0	0.5	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	2.30	%	0.3	6.2	.	Normal
	Day 0	2021-11-10	Yes	1.30	%	0.3	6.2	.	Normal
	Day 14	2021-11-26	Yes	2.40	%	0.3	6.2	.	Normal
	Day 28	2021-12-09	Yes	1.80	%	0.3	6.2	.	Normal
	Day 42	2021-12-28	Yes	3.20	%	0.3	6.2	.	Normal
	Day 56	2022-02-22	Yes	2.50	%	0.3	6.2	.	Normal
05-002	Screening	2021-10-29	Yes	1.10	%	0.3	6.2	.	Normal
	Day 0	2021-11-30	Yes	1.60	%	0.3	6.2	.	Normal
	Day 14	2021-12-14	Yes	2.20	%	0.3	6.2	.	Normal
	Day 28	2021-12-30	Yes	2.70	%	0.3	6.2	.	Normal
	Day 42	2022-01-15	Yes	1.30	%	0.3	6.2	.	Normal
	Day 56	2022-02-03	Yes	2.00	%	0.3	6.2	.	Normal
06-001	Screening	2021-12-15	Yes	2.70	%	0.0	5.4	.	Normal
06-002	Screening	2021-12-15	Yes	3.70	%	0.0	5.4	.	Not Clinically Significant

Listing 6.8 - Study IP-001-09 : Haematology - Lymphocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	2.24	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-11-13	Yes	2.28	10^3/uL	1.1	3.0	.	Normal
	Day 14	2019-11-28	Yes	2.54	10^3/uL	1.1	3.0	.	Normal
	Day 28	2019-12-12	Yes	1.82	10^3/uL	1.1	3.0	.	Normal
	Day 42	2019-12-23	Yes	2.08	10^3/uL	1.1	3.0	.	Normal
	Day 56	2020-01-07	Yes	1.81	10^3/uL	1.1	3.0	.	Normal
01-002	Screening	2018-11-13	Yes	28.04	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	26.73	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	30.19	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	26.84	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	27.81	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	25.78	10^3/uL	1.1	3.0	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	1.66	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-12-11	Yes	1.75	10^3/uL	1.1	3.0	.	Normal
	Day 14	2019-12-27	Yes	1.36	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-01-10	Yes	1.15	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-01-22	Yes	1.37	10^3/uL	1.1	3.0	.	Normal
	Day 56	2020-02-05	Yes	1.64	10^3/uL	1.1	3.0	.	Normal
01-004	Screening	2019-11-15	Yes	1.21	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-12-13	Yes	1.18	10^3/uL	1.1	3.0	.	Normal
	Day 14	2019-12-27	Yes	0.99	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	1.17	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-01-23	Yes	1.08	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	1.07	10^3/uL	1.1	3.0	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	0.99	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	0.83	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	0.68	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	0.96	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	1.03	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	1.15	10^3/uL	1.1	3.0	.	Normal
01-006	Screening	2019-11-20	Yes	1.36	10^3/uL	1.1	3.0	.	Normal

Listing 6.8 - Study IP-001-09 : Haematology - Lymphocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	1.29	10^3/uL	1.1	3.0	.	Normal
	Day 14	2020-01-03	Yes	1.34	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-01-15	Yes	1.25	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-01-29	Yes	1.01	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	1.19	10^3/uL	1.1	3.0	.	Normal
01-007	Screening	2019-11-21	Yes	1.15	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-12-19	Yes	1.19	10^3/uL	1.1	3.0	.	Normal
	Day 14	2020-01-03	Yes	1.14	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-01-16	Yes	1.11	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-01-30	Yes	1.18	10^3/uL	1.1	3.0	.	Normal
	Day 56	2020-02-13	Yes	1.44	10^3/uL	1.1	3.0	.	Normal
01-008	Screening	2019-11-21	Yes	1.54	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-12-19	Yes	1.28	10^3/uL	1.1	3.0	.	Normal
	Day 14	2020-01-03	Yes	2.18	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-01-16	Yes	1.34	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-01-30	Yes	1.60	10^3/uL	1.1	3.0	.	Normal
	Day 56	2020-02-13	Yes	1.66	10^3/uL	1.1	3.0	.	Normal
01-009	Screening	2019-11-26	Yes	1.43	10^3/uL	1.1	3.0	.	Normal
	Day 0	2019-12-23	Yes	1.38	10^3/uL	1.1	3.0	.	Normal
	Day 14	2020-01-07	Yes	1.15	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-01-21	Yes	1.23	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-02-04	Yes	1.07	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	1.32	10^3/uL	1.1	3.0	.	Normal
01-010	Screening	2019-12-10	Yes	0.80	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	0.69	10^3/uL	1.1	3.0	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	1.40	10^3/uL	1.1	3.0	.	Normal
	Day 0	2020-03-05	Yes	1.06	10^3/uL	1.1	3.0	.	Not Clinically Significant

Listing 6.8 - Study IP-001-09 : Haematology - Lymphocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	1.40	10^3/uL	1.1	3.0	.	Normal
	Day 28	2020-04-02	Yes	1.20	10^3/uL	1.1	3.0	.	Normal
	Day 42	2020-04-16	Yes	1.44	10^3/uL	1.1	3.0	.	Normal
	Day 56	2020-04-30	Yes	1.14	10^3/uL	1.1	3.0	.	Normal
05-001	Screening	2021-10-13	No	26.90	%	14.1	45.8	.	Normal
	Day 0	2021-11-10	Yes	29.60	%	14.1	45.8	.	Normal
	Day 14	2021-11-26	Yes	24.80	%	14.1	45.8	.	Normal
	Day 28	2021-12-09	Yes	27.30	%	14.1	45.8	.	Normal
	Day 42	2021-12-28	Yes	30.20	%	14.1	45.8	.	Normal
	Day 56	2022-02-22	Yes	20.40	%	14.1	45.8	.	Normal
05-002	Screening	2021-10-29	Yes	9.00	%	14.1	45.8	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	11.50	%	14.1	45.8	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	18.70	%	14.1	45.8	.	Normal
	Day 28	2021-12-30	Yes	15.20	%	14.1	45.8	.	Normal
	Day 42	2022-01-15	Yes	13.90	%	14.1	45.8	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	17.60	%	14.1	45.8	.	Normal
06-001	Screening	2021-12-15	Yes	17.20	%	20.0	40.0	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	27.10	%	20.0	40.0	.	Not Clinically Significant

Listing 6.9 - Study IP-001-09 : Haematology - Monocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	0.67	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-11-13	Yes	0.77	10^3/uL	0.2	0.96	.	Normal
	Day 14	2019-11-28	Yes	0.85	10^3/uL	0.2	0.96	.	Normal
	Day 28	2019-12-12	Yes	0.81	10^3/uL	0.2	0.96	.	Normal
	Day 42	2019-12-23	Yes	0.82	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-01-07	Yes	0.85	10^3/uL	0.2	0.96	.	Normal
01-002	Screening	2018-11-13	Yes	0.52	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-11	Yes	0.51	10^3/uL	0.2	0.96	.	Normal
	Day 14	2019-12-27	Yes	1.28	10^3/uL	0.2	0.96	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	0.84	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-22	Yes	0.41	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-05	Yes	0.53	10^3/uL	0.2	0.96	.	Normal
01-003	Screening	2019-11-13	Yes	0.35	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-11	Yes	0.48	10^3/uL	0.2	0.96	.	Normal
	Day 14	2019-12-27	Yes	0.43	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-10	Yes	0.51	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-22	Yes	0.32	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-05	Yes	0.33	10^3/uL	0.2	0.96	.	Normal
01-004	Screening	2019-11-15	Yes	0.43	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-13	Yes	0.81	10^3/uL	0.2	0.96	.	Normal
	Day 14	2019-12-27	Yes	0.43	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-09	Yes	0.54	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-23	Yes	0.59	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-10	Yes	0.56	10^3/uL	0.2	0.96	.	Normal
01-005	Screening	2019-11-15	Yes	0.61	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-13	Yes	0.56	10^3/uL	0.2	0.96	.	Normal
	Day 14	2019-12-27	Yes	0.46	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-10	Yes	0.49	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-24	Yes	0.59	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-07	Yes	0.61	10^3/uL	0.2	0.96	.	Normal
01-006	Screening	2019-11-20	Yes	0.76	10^3/uL	0.2	0.96	.	Normal

Listing 6.9 - Study IP-001-09 : Haematology - Monocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	0.63	10^3/uL	0.2	0.96	.	Normal
	Day 14	2020-01-03	Yes	0.61	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-15	Yes	0.62	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-29	Yes	0.77	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-12	Yes	0.69	10^3/uL	0.2	0.96	.	Normal
01-007	Screening	2019-11-21	Yes	0.61	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-19	Yes	1.02	10^3/uL	0.2	0.96	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	0.86	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-16	Yes	0.85	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-30	Yes	0.90	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-13	Yes	0.90	10^3/uL	0.2	0.96	.	Normal
01-008	Screening	2019-11-21	Yes	0.66	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-19	Yes	0.49	10^3/uL	0.2	0.96	.	Normal
	Day 14	2020-01-03	Yes	0.78	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-16	Yes	0.64	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-01-30	Yes	0.64	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-13	Yes	0.64	10^3/uL	0.2	0.96	.	Normal
01-009	Screening	2019-11-26	Yes	0.54	10^3/uL	0.2	0.96	.	Normal
	Day 0	2019-12-23	Yes	0.57	10^3/uL	0.2	0.96	.	Normal
	Day 14	2020-01-07	Yes	0.54	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-01-21	Yes	0.54	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-02-04	Yes	0.53	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-02-18	Yes	0.61	10^3/uL	0.2	0.96	.	Normal
01-010	Screening	2019-12-10	Yes	0.33	10^3/uL	0.2	0.96	.	Normal
	Day 0	2020-01-08	Yes	0.30	10^3/uL	0.2	0.96	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	0.72	10^3/uL	0.2	0.96	.	Normal
	Day 0	2020-03-05	Yes	0.46	10^3/uL	0.2	0.96	.	Normal

Listing 6.9 - Study IP-001-09 : Haematology - Monocytes

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	0.66	10^3/uL	0.2	0.96	.	Normal
	Day 28	2020-04-02	Yes	0.66	10^3/uL	0.2	0.96	.	Normal
	Day 42	2020-04-16	Yes	0.75	10^3/uL	0.2	0.96	.	Normal
	Day 56	2020-04-30	Yes	0.68	10^3/uL	0.2	0.96	.	Normal
05-001	Screening	2021-10-13	No	11.60	%	3.3	9.20	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	18.50	%	3.3	9.20	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	10.10	%	3.3	9.20	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	9.30	%	3.3	9.20	.	Not Clinically Significant
	Day 42	2021-12-28	Yes	10.10	%	3.3	9.20	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	9.30	%	3.3	9.20	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	7.60	%	3.3	9.20	.	Normal
	Day 0	2021-11-30	Yes	8.00	%	3.3	9.20	.	Normal
	Day 14	2021-12-14	Yes	7.50	%	3.3	9.20	.	Normal
	Day 28	2021-12-30	Yes	7.50	%	3.3	9.20	.	Normal
	Day 42	2022-01-15	Yes	9.20	%	3.3	9.20	.	Normal
	Day 56	2022-02-03	Yes	9.00	%	3.3	9.20	.	Normal
06-001	Screening	2021-12-15	Yes	9.10	%	2.0	10.00	.	Normal
06-002	Screening	2021-12-15	Yes	2.80	%	2.0	10.00	.	Normal

Listing 6.10 - Study IP-001-09 : Haematology - Platelets count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	153	10^3/mmc	150	450	.	Normal
	Day 0	2019-11-13	Yes	159	10^3/mmc	150	450	.	Normal
	Day 14	2019-11-28	Yes	170	10^3/mmc	150	450	.	Normal
	Day 28	2019-12-12	Yes	178	10^3/mmc	150	450	.	Normal
	Day 42	2019-12-23	Yes	172	10^3/mmc	150	450	.	Normal
	Day 56	2020-01-07	Yes	152	10^3/mmc	150	450	.	Normal
01-002	Screening	2018-11-13	Yes	139	10^3/mmc	150	450	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	132	10^3/mmc	150	450	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	122	10^3/mmc	150	450	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	134	10^3/mmc	150	450	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	173	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-05	Yes	133	10^3/mmc	150	450	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	180	10^3/mmc	150	450	.	Normal
	Day 0	2019-12-11	Yes	208	10^3/mmc	150	450	.	Normal
	Day 14	2019-12-27	Yes	161	10^3/mmc	150	450	.	Normal
	Day 28	2020-01-10	Yes	221	10^3/mmc	150	450	.	Normal
	Day 42	2020-01-22	Yes	231	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-05	Yes	191	10^3/mmc	150	450	.	Normal
01-004	Screening	2019-11-15	Yes	299	10^3/mmc	150	450	.	Normal
	Day 0	2019-12-13	Yes	301	10^3/mmc	150	450	.	Normal
	Day 14	2019-12-27	Yes	342	10^3/mmc	150	450	.	Normal
	Day 28	2020-01-09	Yes	344	10^3/mmc	150	450	.	Normal
	Day 42	2020-01-23	Yes	243	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-10	Yes	314	10^3/mmc	150	450	.	Normal
01-005	Screening	2019-11-15	Yes	228	10^3/mmc	150	450	.	Normal
	Day 0	2019-12-13	Yes	226	10^3/mmc	150	450	.	Normal
	Day 14	2019-12-27	Yes	224	10^3/mmc	150	450	.	Normal
	Day 28	2020-01-10	Yes	288	10^3/mmc	150	450	.	Normal
	Day 42	2020-01-24	Yes	257	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-07	Yes	252	10^3/mmc	150	450	.	Normal
01-006	Screening	2019-11-20	Yes	225	10^3/mmc	150	450	.	Normal

Listing 6.10 - Study IP-001-09 : Haematology - Platelets count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	225	10^3/mmc	150	450	.	Normal
	Day 14	2020-01-03	Yes	226	10^3/mmc	150	450	.	Normal
	Day 28	2020-01-15	Yes	247	10^3/mmc	150	450	.	Normal
	Day 42	2020-01-29	Yes	204	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-12	Yes	214	10^3/mmc	150	450	.	Normal
01-007	Screening	2019-11-21	Yes	236	10^3/mmc	150	450	.	Normal
	Day 0	2019-12-19	Yes	299	10^3/mmc	150	450	.	Normal
	Day 14	2020-01-03	Yes	288	10^3/mmc	150	450	.	Normal
	Day 28	2020-01-16	Yes	231	10^3/mmc	150	450	.	Normal
	Day 42	2020-01-30	Yes	289	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-13	Yes	312	10^3/mmc	150	450	.	Normal
01-008	Screening	2019-11-21	Yes	256	10^3/mmc	150	450	.	Normal
	Day 0	2019-12-19	Yes	263	10^3/mmc	150	450	.	Normal
	Day 14	2020-01-03	Yes	333	10^3/mmc	150	450	.	Normal
	Day 28	2020-01-16	Yes	305	10^3/mmc	150	450	.	Normal
	Day 42	2020-01-30	Yes	260	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-13	Yes	399	10^3/mmc	150	450	.	Normal
01-009	Screening	2019-11-26	Yes	234	10^3/mmc	150	450	.	Normal
	Day 0	2019-12-23	Yes	216	10^3/mmc	150	450	.	Normal
	Day 14	2020-01-07	Yes	214	10^3/mmc	150	450	.	Normal
	Day 28	2020-01-21	Yes	234	10^3/mmc	150	450	.	Normal
	Day 42	2020-02-04	Yes	218	10^3/mmc	150	450	.	Normal
	Day 56	2020-02-18	Yes	233	10^3/mmc	150	450	.	Normal
01-010	Screening	2019-12-10	Yes	116	10^3/mmc	150	450	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	117	10^3/mmc	150	450	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	209	10^3/mmc	150	450	.	Normal
	Day 0	2020-03-05	Yes	187	10^3/mmc	150	450	.	Normal

Listing 6.10 - Study IP-001-09 : Haematology - Platelets count

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	205	10^3/mmc	150	450	.	Normal
	Day 28	2020-04-02	Yes	226	10^3/mmc	150	450	.	Normal
	Day 42	2020-04-16	Yes	215	10^3/mmc	150	450	.	Normal
	Day 56	2020-04-30	Yes	226	10^3/mmc	150	450	.	Normal
05-001	Screening	2021-10-13	No	229	10^3/uL	179	373	.	Normal
	Day 0	2021-11-10	Yes	242	10^3/uL	179	373	.	Normal
	Day 14	2021-11-26	Yes	315	10^3/uL	179	373	.	Normal
	Day 28	2021-12-09	Yes	293	10^3/uL	179	373	.	Normal
	Day 42	2021-12-28	Yes	301	10^3/uL	179	373	.	Normal
	Day 56	2022-02-22	Yes	317	10^3/uL	179	373	.	Normal
05-002	Screening	2021-10-29	Yes	367	10^3/uL	179	373	.	Normal
	Day 0	2021-11-30	Yes	349	10^3/uL	179	373	.	Normal
	Day 14	2021-12-14	Yes	328	10^3/uL	179	373	.	Normal
	Day 28	2021-12-30	Yes	243	10^3/uL	179	373	.	Normal
	Day 42	2022-01-15	Yes	287	10^3/uL	179	373	.	Normal
	Day 56	2022-02-03	Yes	330	10^3/uL	179	373	.	Normal
06-001	Screening	2021-12-15	Yes	162	10^9/L	150	450	.	Normal
06-002	Screening	2021-12-15	Yes	207	10^9/L	150	450	.	Not Clinically Significant

Listing 7.1 - Study IP-001-09 : Biochemistry - BUN

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	75.80	mg/dL	9	20.0	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	79.70	mg/dL	9	20.0	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	82.10	mg/dL	9	20.0	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	81.20	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	81.20	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	81.20	mg/dL	18	55.0	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	75.50	mg/dL	9	20.0	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	169.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	112.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	83.54	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	84.94	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	72.80	mg/dL	18	55.0	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	99.80	mg/dL	9	20.0	.	Clinically significant for concomitant disease
	Day 0	2019-12-11	Yes	219.00	mg/dL	19	44.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	215.00	mg/dL	19	44.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	186.00	mg/dL	19	44.0	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	178.00	mg/dL	19	44.0	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	154.00	mg/dL	19	44.0	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	83.70	mg/dL	7	17.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	163.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	201.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	190.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	195.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	192.00	mg/dL	21	42.8	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	52.00	mg/dL	9	20.0	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	164.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	119.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	113.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	122.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	127.00	mg/dL	18	55.0	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	65.20	mg/dL	9	20.0	.	Not Clinically Significant

Listing 7.1 - Study IP-001-09 : Biochemistry - BUN

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	113.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	133.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	112.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	103.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	132.00	mg/dL	18	55.0	.	Not Clinically Significant
01-007	Screening	2019-11-21	No	83.80	mg/dL	9	20.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	202.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	225.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	245.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	209.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	188.00	mg/dL	18	55.0	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	106.40	mg/dL	9	20.0	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	201.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	96.60	mg/dL	18	55.0	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	98.94	mg/dL	18	55.0	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	86.80	mg/dL	18	55.0	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	80.27	mg/dL	18	55.0	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	77.00	mg/dL	7	17.0	.	Clinically sign. for the pathology under study
	Day 0	2019-12-23	Yes	179.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	207.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	168.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	181.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	169.00	mg/dL	21	42.8	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	91.12	mg/dL	18	55.0	.	Clinically sign. for the pathology under study
	Day 0	2020-01-08	Yes	230.00	mg/dL	18	55.0	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	81.77	mg/dL	21	42.8	.	Clinically sign. for the pathology under study
	Day 0	2020-03-05	Yes	74.20	mg/dL	21	42.8	.	Not Clinically Significant

Listing 7.1 - Study IP-001-09 : Biochemistry - BUN

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	159.00	mg/dL	21	42.8	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	87.74	mg/dL	21	42.8	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	98.47	mg/dL	21	42.8	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	86.80	mg/dL	21	42.8	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	194.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	177.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	260.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	246.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	228.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	232.00	mg/dL	15	38.0	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	163.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	165.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	149.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	182.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	157.00	mg/dL	15	38.0	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	156.00	mg/dL	15	38.0	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	75.00	mg/dL	10	23.0	.	Clinically significant for concomitant disease
06-002	Screening	2021-12-15	Yes	64.00	mg/dL	10	23.0	.	Clinically significant for concomitant disease

Listing 7.2 - Study IP-001-09 : Biochemistry - Creatinine

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	9.15	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	8.25	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	9.21	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	8.82	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	8.59	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	8.95	mg/dL	0.72	1.25	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	7.07	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	6.97	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	7.92	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	7.23	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	6.96	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	7.19	mg/dL	0.72	1.25	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	12.35	mg/dL	0.66	1.25	.	Clinically significant for concomitant disease
	Day 0	2019-12-11	Yes	12.83	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	14.12	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	12.71	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	12.07	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	11.80	mg/dL	0.72	1.25	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	8.23	mg/dL	0.52	1.04	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	8.82	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	9.31	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	8.74	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	9.11	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	10.17	mg/dL	0.57	1.11	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	7.24	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	9.96	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	7.58	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	8.04	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	8.04	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	7.55	mg/dL	0.72	1.25	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	6.80	mg/dL	0.66	1.25	.	Not Clinically Significant

Listing 7.2 - Study IP-001-09 : Biochemistry - Creatinine

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	6.54	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	6.63	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	6.29	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	6.72	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	6.74	mg/dL	0.72	1.25	.	Not Clinically Significant
01-007	Screening	2019-11-21	No	8.00	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	9.00	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	8.63	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	10.00	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	10.93	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	11.24	mg/dL	0.72	1.25	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	11.08	mg/dL	0.66	1.25	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	10.44	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	10.87	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	10.44	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	11.07	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	10.75	mg/dL	0.72	1.25	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	7.07	mg/dL	0.52	1.04	.	Clinically sign. for the pathology under study
	Day 0	2019-12-23	Yes	5.64	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	6.12	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	5.42	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	6.12	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	5.71	mg/dL	0.57	1.11	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	7.85	mg/dL	0.72	1.25	.	Clinically sign. for the pathology under study
	Day 0	2020-01-08	Yes	8.26	mg/dL	0.72	1.25	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	6.25	mg/dL	0.57	1.11	.	Clinically sign. for the pathology under study
	Day 0	2020-03-05	Yes	5.65	mg/dL	0.57	1.11	.	Not Clinically Significant

Listing 7.2 - Study IP-001-09 : Biochemistry - Creatinine

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	5.65	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	6.25	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	6.83	mg/dL	0.57	1.11	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	6.42	mg/dL	0.57	1.11	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	6.57	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	7.76	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	7.62	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	7.39	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	7.28	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	8.41	mg/dL	0.67	1.17	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	7.78	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	7.98	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	8.36	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	8.87	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	8.38	mg/dL	0.67	1.17	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	8.02	mg/dL	0.67	1.17	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	10.00	mg/dL	0.67	1.17	.	Clinically significant for concomitant disease
06-002	Screening	2021-12-15	Yes	8.40	mg/dL	0.67	1.17	.	Clinically significant for concomitant disease

Listing 7.3 - Study IP-001-09 : Biochemistry - Glucose

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	90	mg/dL	74	106	.	Normal
	Day 0	2019-11-13	Yes	89	mg/dL	74	106	.	Normal
	Day 14	2019-11-28	Yes	98	mg/dL	74	106	.	Normal
	Day 28	2019-12-12	Yes	92	mg/dL	80	115	.	Normal
	Day 42	2019-12-23	Yes	109	mg/dL	80	115	.	Normal
	Day 56	2020-01-07	Yes	130	mg/dL	80	115	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	148	mg/dL	74	106	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	138	mg/dL	80	115	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	136	mg/dL	80	115	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	222	mg/dL	80	115	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	113	mg/dL	80	115	.	Normal
	Day 56	2020-02-05	Yes	193	mg/dL	80	115	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	87	mg/dL	74	106	.	Normal
	Day 0	2019-12-11	Yes	87	mg/dl	70	105	.	Normal
	Day 14	2019-12-27	Yes	82	mg/dl	70	105	.	Normal
	Day 28	2020-01-10	Yes	124	mg/dl	70	105	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	86	mg/dl	70	105	.	Normal
	Day 56	2020-02-05	Yes	126	mg/dl	70	105	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	104	mg/dL	74	106	.	Normal
	Day 0	2019-12-13	Yes	148	mg/dL	71	99	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	98	mg/dL	71	99	.	Normal
	Day 28	2020-01-09	Yes	107	mg/dL	71	99	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	95	mg/dL	71	99	.	Normal
	Day 56	2020-02-10	Yes	130	mg/dL	71	99	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	131	mg/dL	74	106	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	131	mg/dL	80	115	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	112	mg/dL	80	115	.	Normal
	Day 28	2020-01-10	Yes	166	mg/dL	80	115	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	167	mg/dL	80	115	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	109	mg/dL	80	115	.	Normal
01-006	Screening	2019-11-20	Yes	82	mg/dL	74	106	.	Normal

Listing 7.3 - Study IP-001-09 : Biochemistry - Glucose

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	71	mg/dL	80	115	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	73	mg/dL	80	115	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	113	mg/dL	80	115	.	Normal
	Day 42	2020-01-29	Yes	85	mg/dL	80	115	.	Normal
	Day 56	2020-02-12	Yes	112	mg/dL	80	115	.	Normal
01-007	Screening	2019-11-21	No	199	mg/dL	74	106	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	127	mg/dL	80	115	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	95	mg/dL	80	115	.	Normal
	Day 28	2020-01-16	Yes	115	mg/dL	80	115	.	Normal
	Day 42	2020-01-30	Yes	105	mg/dL	80	115	.	Normal
	Day 56	2020-02-13	Yes	89	mg/dL	80	115	.	Normal
01-008	Screening	2019-11-21	Yes	88	mg/dL	74	106	.	Normal
	Day 0	2019-12-19	Yes	141	mg/dl	70	105	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	90	mg/dl	70	105	.	Normal
	Day 28	2020-01-16	Yes	122	mg/dl	70	105	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	100	mg/dl	70	105	.	Normal
	Day 56	2020-02-13	Yes	83	mg/dl	70	105	.	Normal
01-009	Screening	2019-11-26	Yes	93	mg/dL	74	106	.	Normal
	Day 0	2019-12-23	Yes	94	mg/dL	71	99	.	Normal
	Day 14	2020-01-07	Yes	98	mg/dL	71	99	.	Normal
	Day 28	2020-01-21	Yes	108	mg/dL	71	99	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	86	mg/dL	71	99	.	Normal
	Day 56	2020-02-18	Yes	93	mg/dL	71	99	.	Normal
01-010	Screening	2019-12-12	Yes	78	mg/dL	80	115	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	98	mg/dL	80	115	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	75	mg/dL	71	99	.	Normal
	Day 0	2020-03-05	Yes	78	mg/dL	71	99	.	Normal

Listing 7.3 - Study IP-001-09 : Biochemistry - Glucose

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	84	mg/dL	71	99	.	Normal
	Day 28	2020-04-02	Yes	83	mg/dL	71	99	.	Normal
	Day 42	2020-04-16	Yes	78	mg/dL	71	99	.	Normal
	Day 56	2020-04-30	Yes	136	mg/dL	71	99	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	100	mg/dL	0	100	.	Normal
	Day 0	2021-11-10	Yes	95	mg/dL	0	100	.	Normal
	Day 14	2021-11-26	Yes	93	mg/dL	0	100	.	Normal
	Day 28	2021-12-09	Yes	101	mg/dL	0	100	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	108	mg/dL	0	100	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	107	mg/dL	0	100	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	155	mg/dL	0	100	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	137	mg/dL	0	100	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	127	mg/dL	0	100	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	179	mg/dL	0	100	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	147	mg/dL	0	100	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	88	mg/dL	0	100	.	Normal
06-001	Screening	2021-12-15	Yes	60	mg/dL	65	100	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	73	mg/dL	65	100	.	Not Clinically Significant

Listing 7.4 - Study IP-001-09 : Biochemistry - Total Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-001	Screening	2019-10-16	Yes	.	mg/dl	0	200	Yes		.
	Day 0	2019-11-13	Yes	149	mg/dl	0	200	.	Normal	
	Day 14	2019-11-28	Yes	150	mg/dl	0	200	.	Normal	
	Day 28	2019-12-12	Yes	135	mg/dl	0	200	.	Normal	
	Day 42	2019-12-23	Yes	153	mg/dl	0	200	.	Normal	
	Day 56	2020-01-07	Yes	.	mg/dl	0	200	Yes		.
01-002	Screening	2019-11-13	Yes	123	mg/dl	0	200	.	Normal	
	Day 0	2019-12-11	Yes	113	mg/dl	0	200	.	Normal	
	Day 14	2019-12-27	Yes	121	mg/dl	0	200	.	Normal	
	Day 28	2020-01-08	Yes	123	mg/dl	0	200	.	Normal	
	Day 42	2020-01-22	Yes	117	mg/dl	0	200	.	Normal	
	Day 56	2020-02-05	Yes	120	mg/dl	0	200	.	Normal	
01-003	Screening	2019-11-13	Yes	147	mg/dl	0	200	.	Normal	
	Day 0	2019-12-11	Yes	134	mg/dl	0	200	.	Normal	
	Day 14	2019-12-27	Yes	141	mg/dl	0	200	.	Normal	
	Day 28	2020-01-10	Yes	142	mg/dl	0	200	.	Normal	
	Day 42	2020-01-22	Yes	141	mg/dl	0	200	.	Normal	
	Day 56	2020-02-05	Yes	158	mg/dl	0	200	.	Normal	
01-004	Screening	2019-11-15	Yes	143	mg/dl	0	200	.	Normal	
	Day 0	2019-12-13	Yes	143	mg/dl	0	200	.	Normal	
	Day 14	2019-12-27	Yes	147	mg/dl	0	200	.	Normal	
	Day 28	2020-01-09	Yes	141	mg/dl	0	200	.	Normal	
	Day 42	2020-01-23	Yes	144	mg/dl	0	200	.	Normal	
	Day 56	2020-02-10	Yes	144	mg/dl	0	200	.	Normal	
01-005	Screening	2019-11-15	Yes	231	mg/dl	0	200	.	Not Clinically Significant	
	Day 0	2019-12-13	Yes	163	mg/dl	0	200	.	Normal	
	Day 14	2019-12-27	Yes	186	mg/dl	0	200	.	Normal	
	Day 28	2020-01-10	Yes	245	mg/dl	0	200	.	Not Clinically Significant	
	Day 42	2020-01-24	Yes	277	mg/dl	0	200	.	Not Clinically Significant	
	Day 56	2020-02-07	Yes	236	mg/dl	0	200	.	Not Clinically Significant	
01-006	Screening	2019-11-20	Yes	175	mg/dl	0	200	.	Normal	

Listing 7.4 - Study IP-001-09 : Biochemistry - Total Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	182	mg/dl	0	200	.	Normal
	Day 14	2020-01-03	Yes	220	mg/dl	0	200	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	194	mg/dl	0	200	.	Normal
	Day 42	2020-01-29	Yes	185	mg/dl	0	200	.	Normal
	Day 56	2020-02-12	Yes	193	mg/dl	0	200	.	Normal
01-007	Screening	2019-11-21	No	237	mg/dl	0	200	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	180	mg/dl	0	200	.	Normal
	Day 14	2020-01-03	Yes	199	mg/dl	0	200	.	Normal
	Day 28	2020-01-16	Yes	136	mg/dl	0	200	.	Normal
	Day 42	2020-01-30	Yes	157	mg/dl	0	200	.	Normal
	Day 56	2020-02-13	Yes	134	mg/dl	0	200	.	Normal
01-008	Screening	2019-11-21	Yes	138	mg/dl	0	200	.	Normal
	Day 0	2019-12-19	Yes	133	mg/dl	0	200	.	Normal
	Day 14	2020-01-03	Yes	131	mg/dl	0	200	.	Normal
	Day 28	2020-01-16	Yes	133	mg/dl	0	200	.	Normal
	Day 42	2020-01-30	Yes	133	mg/dl	0	200	.	Normal
	Day 56	2020-02-13	Yes	125	mg/dl	0	200	.	Normal
01-009	Screening	2019-11-26	Yes	172	mg/dl	0	200	.	Normal
	Day 0	2019-12-23	Yes	196	mg/dl	0	200	.	Normal
	Day 14	2020-01-07	Yes	191	mg/dl	0	200	.	Normal
	Day 28	2020-01-21	Yes	183	mg/dl	0	200	.	Normal
	Day 42	2020-02-04	Yes	198	mg/dl	0	200	.	Normal
	Day 56	2020-02-18	Yes	198	mg/dl	0	200	.	Normal
01-010	Screening	2019-12-12	Yes	108	mg/dl	0	200	.	Normal
	Day 0	2020-01-08	Yes	102	mg/dl	0	200	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	161	mg/dl	0	200	.	Normal
	Day 0	2020-03-05	Yes	166	mg/dl	0	200	.	Normal

Listing 7.4 - Study IP-001-09 : Biochemistry - Total Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	145	mg/dl	0	200	.	Normal
	Day 28	2020-04-02	Yes	157	mg/dl	0	200	.	Normal
	Day 42	2020-04-16	Yes	174	mg/dl	0	200	.	Normal
	Day 56	2020-04-30	Yes	152	mg/dl	0	200	.	Normal
05-001	Screening	2021-10-13	No	185	mg/dL	0	200	.	Normal
	Day 0	2021-11-10	Yes	156	mg/dL	0	200	.	Normal
	Day 14	2021-11-26	Yes	172	mg/dL	0	200	.	Normal
	Day 28	2021-12-09	Yes	161	mg/dL	0	200	.	Normal
	Day 42	2022-01-28	Yes	178	mg/dL	0	200	.	Normal
	Day 56	2022-02-22	Yes	191	mg/dL	0	200	.	Normal
05-002	Screening	2021-10-29	Yes	157	mg/dL	0	200	.	Normal
	Day 0	2021-11-30	Yes	142	mg/dL	0	200	.	Normal
	Day 14	2021-12-14	Yes	113	mg/dL	0	200	.	Normal
	Day 28	2021-12-30	Yes	109	mg/dL	0	200	.	Normal
	Day 42	2022-01-15	Yes	128	mg/dL	0	200	.	Normal
	Day 56	2022-02-03	Yes	110	mg/dL	0	200	.	Normal
06-001	Screening	2021-12-15	Yes	130	mg/dL	130	200	.	Normal
06-002	Screening	2021-12-15	Yes	160	mg/dL	130	200	.	Not Clinically Significant

Listing 7.5 - Study IP-001-09 : Biochemistry - HDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-001	Screening	2019-10-16	Yes	.	mg/dl	40	60	Yes		.
	Day 0	2019-11-13	Yes	49	mg/dl	40	60	.	Normal	
	Day 14	2019-11-28	Yes	54	mg/dl	40	60	.	Normal	
	Day 28	2019-12-12	Yes	47	mg/dl	40	60	.	Normal	
	Day 42	2019-12-23	Yes	52	mg/dl	40	60	.	Normal	
	Day 56	2020-01-07	Yes	.	mg/dl	40	60	Yes		.
01-002	Screening	2019-11-13	Yes	37	mg/dl	40	60	.	Not Clinically Significant	
	Day 0	2019-12-11	Yes	39	mg/dl	40	60	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	38	mg/dl	40	60	.	Not Clinically Significant	
	Day 28	2020-01-08	Yes	40	mg/dl	40	60	.	Normal	
	Day 42	2020-01-22	Yes	35	mg/dl	40	60	.	Not Clinically Significant	
	Day 56	2020-02-05	Yes	38	mg/dl	40	60	.	Not Clinically Significant	
01-003	Screening	2019-11-13	Yes	26	mg/dl	40	60	.	Not Clinically Significant	
	Day 0	2019-12-11	Yes	25	mg/dl	40	60	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	29	mg/dl	40	60	.	Not Clinically Significant	
	Day 28	2020-01-10	Yes	31	mg/dl	40	60	.	Not Clinically Significant	
	Day 42	2020-01-22	Yes	30	mg/dl	40	60	.	Not Clinically Significant	
	Day 56	2020-02-05	Yes	33	mg/dl	40	60	.	Not Clinically Significant	
01-004	Screening	2019-11-15	Yes	48	mg/dl	40	60	.	Normal	
	Day 0	2019-12-13	Yes	52	mg/dl	40	60	.	Normal	
	Day 14	2019-12-27	Yes	50	mg/dl	40	60	.	Normal	
	Day 28	2020-01-09	Yes	56	mg/dl	40	60	.	Normal	
	Day 42	2020-01-23	Yes	51	mg/dl	40	60	.	Normal	
	Day 56	2020-02-10	Yes	48	mg/dl	40	60	.	Normal	
01-005	Screening	2019-11-15	Yes	30	mg/dl	40	60	.	Not Clinically Significant	
	Day 0	2019-12-13	Yes	27	mg/dl	40	60	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	28	mg/dl	40	60	.	Not Clinically Significant	
	Day 28	2020-01-10	Yes	27	mg/dl	40	60	.	Not Clinically Significant	
	Day 42	2020-01-24	Yes	28	mg/dl	40	60	.	Not Clinically Significant	
	Day 56	2020-02-07	Yes	26	mg/dl	40	60	.	Not Clinically Significant	
01-006	Screening	2019-11-20	Yes	25	mg/dl	40	60	.	Not Clinically Significant	

Listing 7.5 - Study IP-001-09 : Biochemistry - HDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	25	mg/dl	40	60	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	32	mg/dl	40	60	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	31	mg/dl	40	60	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	30	mg/dl	40	60	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	31	mg/dl	40	60	.	Not Clinically Significant
01-007	Screening	2019-11-21	No	32	mg/dl	40	60	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	34	mg/dl	40	60	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	31	mg/dl	40	60	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	29	mg/dl	40	60	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	25	mg/dl	40	60	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	26	mg/dl	40	60	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	46	mg/dl	40	60	.	Normal
	Day 0	2019-12-19	Yes	42	mg/dl	40	60	.	Normal
	Day 14	2020-01-03	Yes	36	mg/dl	40	60	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	45	mg/dl	40	60	.	Normal
	Day 42	2020-01-30	Yes	35	mg/dl	40	60	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	35	mg/dl	40	60	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	33	mg/dl	40	60	.	Not Clinically Significant
	Day 0	2019-12-23	Yes	35	mg/dl	40	60	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	38	mg/dl	40	60	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	37	mg/dl	40	60	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	43	mg/dl	40	60	.	Normal
	Day 56	2020-02-18	Yes	39	mg/dl	40	60	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	32	mg/dl	40	60	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	36	mg/dl	40	60	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	44	mg/dl	40	60	.	Normal
	Day 0	2020-03-05	Yes	50	mg/dl	40	60	.	Normal

Listing 7.5 - Study IP-001-09 : Biochemistry - HDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-011	Day 14	2020-03-20	Yes	38	mg/dl	40	60	.	Not Clinically Significant	
	Day 28	2020-04-02	Yes	41	mg/dl	40	60	.	Normal	
	Day 42	2020-04-16	Yes	46	mg/dl	40	60	.	Normal	
	Day 56	2020-04-30	Yes	41	mg/dl	40	60	.	Normal	
05-001	Screening	2021-10-13	No	.	mg/dL	40	200	Yes		.
	Day 0	2021-11-10	Yes	49	mg/dL	40	200	.	Normal	
	Day 14	2021-11-26	Yes	46	mg/dL	40	200	.	Normal	
	Day 28	2021-12-09	Yes	49	mg/dL	40	200	.	Normal	
	Day 42	2022-01-28	Yes	57	mg/dL	40	200	.	Normal	
	Day 56	2022-02-22	Yes	42	mg/dL	40	200	.	Normal	
05-002	Screening	2021-10-29	Yes	75	mg/dL	40	200	.	Normal	
	Day 0	2021-11-30	Yes	78	mg/dL	40	200	.	Normal	
	Day 14	2021-12-14	Yes	54	mg/dL	40	200	.	Normal	
	Day 28	2021-12-30	Yes	47	mg/dL	40	200	.	Normal	
	Day 42	2022-01-15	Yes	56	mg/dL	40	200	.	Normal	
	Day 56	2022-02-03	Yes	49	mg/dL	40	200	.	Normal	
06-001	Screening	2021-12-15	Yes	44	mg/dL	45	200	.	Not Clinically Significant	
06-002	Screening	2021-12-15	Yes	102	mg/dL	45	200	.	Not Clinically Significant	

Listing 7.6 - Study IP-001-09 : Biochemistry - LDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-001	Screening	2019-10-16	Yes	.	mg/dL	0	150	Yes		.
	Day 0	2019-11-13	Yes	72.0	mg/dL	0	150	.	Normal	
	Day 14	2019-11-28	Yes	69.0	mg/dL	0	150	.	Normal	
	Day 28	2019-12-12	Yes	70.0	mg/dL	0	100	.	Normal	
	Day 42	2019-12-23	Yes	84.0	mg/dL	0	100	.	Normal	
	Day 56	2020-01-07	Yes	.	mg/dL	0	100	Yes		.
01-002	Screening	2019-11-13	Yes	69.2	mg/dL	0	150	.	Normal	
	Day 0	2019-12-11	Yes	56.0	mg/dL	0	100	.	Normal	
	Day 14	2019-12-27	Yes	67.0	mg/dL	0	100	.	Normal	
	Day 28	2020-01-08	Yes	61.0	mg/dL	0	100	.	Normal	
	Day 42	2020-01-22	Yes	65.0	mg/dL	0	100	.	Normal	
	Day 56	2020-02-05	Yes	60.0	mg/dL	0	100	.	Normal	
01-003	Screening	2019-11-13	Yes	54.8	mg/dL	0	150	.	Normal	
	Day 0	2019-12-11	Yes	75.0	mg/dL	0	100	.	Normal	
	Day 14	2019-12-27	Yes	72.0	mg/dL	0	100	.	Normal	
	Day 28	2020-01-10	Yes	79.0	mg/dL	0	100	.	Normal	
	Day 42	2020-01-22	Yes	85.0	mg/dL	0	100	.	Normal	
	Day 56	2020-02-05	Yes	83.0	mg/dL	0	100	.	Normal	
01-004	Screening	2019-11-15	Yes	69.2	mg/dL	0	150	.	Normal	
	Day 0	2019-12-13	Yes	70.0	mg/dL	0	100	.	Normal	
	Day 14	2019-12-27	Yes	67.0	mg/dL	0	100	.	Normal	
	Day 28	2020-01-09	Yes	63.0	mg/dL	0	100	.	Normal	
	Day 42	2020-01-23	Yes	85.0	mg/dL	0	100	.	Normal	
	Day 56	2020-02-10	Yes	67.0	mg/dL	0	100	.	Normal	
01-005	Screening	2019-11-15	Yes	149.0	mg/dL	0	150	.	Normal	
	Day 0	2019-12-13	Yes	104.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	117.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 28	2020-01-10	Yes	133.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 42	2020-01-24	Yes	157.0	mg/dL	0	100	.	Not Clinically Significant	
	Day 56	2020-02-07	Yes	141.0	mg/dL	0	100	.	Not Clinically Significant	
01-006	Screening	2019-11-20	Yes	97.8	mg/dL	0	150	.	Normal	

Listing 7.6 - Study IP-001-09 : Biochemistry - LDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	105.0	mg/dL	0	100	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	98.0	mg/dL	0	100	.	Normal
	Day 28	2020-01-15	Yes	97.0	mg/dL	0	100	.	Normal
	Day 42	2020-01-29	Yes	121.0	mg/dL	0	100	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	113.0	mg/dL	0	100	.	Not Clinically Significant
01-007	Screening	2019-11-21	No	100.8	mg/dL	0	150	.	Normal
	Day 0	2019-12-19	Yes	97.0	mg/dL	0	100	.	Normal
	Day 14	2020-01-03	Yes	76.0	mg/dL	0	100	.	Normal
	Day 28	2020-01-16	Yes	75.0	mg/dL	0	100	.	Normal
	Day 42	2020-01-30	Yes	72.0	mg/dL	0	100	.	Normal
	Day 56	2020-02-13	Yes	79.0	mg/dL	0	100	.	Normal
01-008	Screening	2019-11-21	Yes	75.2	mg/dL	0	150	.	Normal
	Day 0	2019-12-19	Yes	73.0	mg/dL	0	100	.	Normal
	Day 14	2020-01-03	Yes	72.0	mg/dL	0	100	.	Normal
	Day 28	2020-01-16	Yes	68.0	mg/dL	0	100	.	Normal
	Day 42	2020-01-30	Yes	69.0	mg/dL	0	100	.	Normal
	Day 56	2020-02-13	Yes	70.0	mg/dL	0	100	.	Normal
01-009	Screening	2019-11-26	Yes	91.4	mg/dL	0	150	.	Normal
	Day 0	2019-12-23	Yes	114.0	mg/dL	0	100	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	117.0	mg/dL	0	100	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	109.0	mg/dL	0	100	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	126.0	mg/dL	0	100	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	126.0	mg/dL	0	100	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	59.4	mg/dL	0	100	.	Normal
	Day 0	2020-01-08	Yes	50.0	mg/dL	0	100	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	95.0	mg/dL	0	100	.	Normal
	Day 0	2020-03-05	Yes	91.0	mg/dL	0	100	.	Normal

Listing 7.6 - Study IP-001-09 : Biochemistry - LDL Cholesterol

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-011	Day 14	2020-03-20	Yes	70.0	mg/dL	0	100	.	Normal	
	Day 28	2020-04-02	Yes	85.0	mg/dL	0	100	.	Normal	
	Day 42	2020-04-16	Yes	96.0	mg/dL	0	100	.	Normal	
	Day 56	2020-04-30	Yes	79.0	mg/dL	0	100	.	Normal	
05-001	Screening	2021-10-13	No	.	mg/dL	0	70	Yes		.
	Day 0	2021-11-10	Yes	72.0	mg/dL	0	70	.	Not Clinically Significant	
	Day 14	2021-11-26	Yes	77.0	mg/dL	0	70	.	Not Clinically Significant	
	Day 28	2021-12-09	Yes	69.0	mg/dL	0	70	.	Normal	
	Day 42	2022-01-28	Yes	91.0	mg/dL	0	70	.	Not Clinically Significant	
	Day 56	2022-02-22	Yes	108.0	mg/dL	0	70	.	Not Clinically Significant	
05-002	Screening	2021-10-29	Yes	60.0	mg/dL	0	70	.	Normal	
	Day 0	2021-11-30	Yes	47.0	mg/dL	0	70	.	Normal	
	Day 14	2021-12-14	Yes	37.0	mg/dL	0	70	.	Normal	
	Day 28	2021-12-30	Yes	43.0	mg/dL	0	70	.	Normal	
	Day 42	2022-01-15	Yes	51.0	mg/dL	0	70	.	Normal	
	Day 56	2022-02-03	Yes	47.0	mg/dL	0	70	.	Normal	
06-001	Screening	2021-12-15	Yes	73.0	mg/dL	0	130	.	Normal	
06-002	Screening	2021-12-15	Yes	47.0	mg/dL	0	130	.	Not Clinically Significant	

Listing 7.7 - Study IP-001-09 : Biochemistry - Triglycerides

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-001	Screening	2019-10-16	Yes	.	mg/dl	70	200	Yes		.
	Day 0	2019-11-13	Yes	144	mg/dl	70	200	.	Normal	
	Day 14	2019-11-28	Yes	.	mg/dl	70	200	Yes		.
	Day 28	2019-12-12	Yes	102	mg/dL	0	150	.	Normal	
	Day 42	2019-12-23	Yes	85	mg/dL	0	150	.	Normal	
	Day 56	2020-01-07	Yes	74	mg/dL	0	150	.	Normal	
01-002	Screening	2019-11-13	Yes	84	mg/dl	70	200	.	Normal	
	Day 0	2019-12-11	Yes	77	mg/dL	0	150	.	Normal	
	Day 14	2019-12-27	Yes	66	mg/dL	0	150	.	Normal	
	Day 28	2020-01-08	Yes	97	mg/dL	0	150	.	Normal	
	Day 42	2020-01-22	Yes	67	mg/dL	0	150	.	Normal	
	Day 56	2020-02-05	Yes	76	mg/dL	0	150	.	Normal	
01-003	Screening	2019-11-13	Yes	331	mg/dl	70	200	.	Not Clinically Significant	
	Day 0	2019-12-11	Yes	189	mg/dL	0	150	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	219	mg/dL	0	150	.	Not Clinically Significant	
	Day 28	2020-01-10	Yes	179	mg/dL	0	150	.	Not Clinically Significant	
	Day 42	2020-01-22	Yes	137	mg/dL	0	150	.	Normal	
	Day 56	2020-02-05	Yes	171	mg/dL	0	150	.	Not Clinically Significant	
01-004	Screening	2019-11-15	Yes	129	mg/dl	70	200	.	Normal	
	Day 0	2019-12-13	Yes	106	mg/dL	0	150	.	Normal	
	Day 14	2019-12-27	Yes	141	mg/dL	0	150	.	Normal	
	Day 28	2020-01-09	Yes	107	mg/dL	0	150	.	Normal	
	Day 42	2020-01-23	Yes	80	mg/dL	0	150	.	Normal	
	Day 56	2020-02-10	Yes	122	mg/dL	0	150	.	Normal	
01-005	Screening	2019-11-15	Yes	260	mg/dl	70	200	.	Not Clinically Significant	
	Day 0	2019-12-13	Yes	131	mg/dL	0	150	.	Normal	
	Day 14	2019-12-27	Yes	169	mg/dL	0	150	.	Not Clinically Significant	
	Day 28	2020-01-10	Yes	.	mg/dL	0	150	Yes		.
	Day 42	2020-01-24	Yes	336	mg/dL	0	150	.	Not Clinically Significant	
	Day 56	2020-02-07	Yes	250	mg/dL	0	150	.	Not Clinically Significant	
01-006	Screening	2019-11-20	Yes	261	mg/dl	70	200	.	Not Clinically Significant	

Listing 7.7 - Study IP-001-09 : Biochemistry - Triglycerides

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	.	mg/dL	0	150	Yes		.
	Day 14	2020-01-03	Yes	319	mg/dL	0	150	.	Not Clinically Significant	
	Day 28	2020-01-15	Yes	257	mg/dL	0	150	.	Not Clinically Significant	
	Day 42	2020-01-29	Yes	165	mg/dL	0	150	.	Not Clinically Significant	
	Day 56	2020-02-12	Yes	178	mg/dL	0	150	.	Not Clinically Significant	
01-007	Screening	2019-11-21	No	521	mg/dl	70	200	.	Not Clinically Significant	
	Day 0	2019-12-19	Yes	364	mg/dL	0	150	.	Not Clinically Significant	
	Day 14	2020-01-03	Yes	808	mg/dL	0	150	.	Not Clinically Significant	
	Day 28	2020-01-16	Yes	344	mg/dL	0	150	.	Not Clinically Significant	
	Day 42	2020-01-30	Yes	300	mg/dL	0	150	.	Not Clinically Significant	
	Day 56	2020-02-13	Yes	174	mg/dL	0	150	.	Not Clinically Significant	
01-008	Screening	2019-11-21	Yes	84	mg/dl	70	200	.	Normal	
	Day 0	2019-12-19	Yes	101	mg/dL	0	150	.	Normal	
	Day 14	2020-01-03	Yes	112	mg/dL	0	150	.	Normal	
	Day 28	2020-01-16	Yes	100	mg/dL	0	150	.	Normal	
	Day 42	2020-01-30	Yes	102	mg/dL	0	150	.	Normal	
	Day 56	2020-02-13	Yes	125	mg/dL	0	150	.	Normal	
01-009	Screening	2019-11-26	Yes	238	mg/dl	70	200	.	Not Clinically Significant	
	Day 0	2019-12-23	Yes	85	mg/dL	0	150	.	Normal	
	Day 14	2020-01-07	Yes	130	mg/dL	0	150	.	Normal	
	Day 28	2020-01-21	Yes	128	mg/dL	0	150	.	Normal	
	Day 42	2020-02-04	Yes	132	mg/dL	0	150	.	Normal	
	Day 56	2020-02-18	Yes	146	mg/dL	0	150	.	Normal	
01-010	Screening	2019-12-12	Yes	83	mg/dL	0	150	.	Normal	
	Day 0	2020-01-08	Yes	83	mg/dL	0	150	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	122	mg/dL	0	150	.	Normal	
	Day 0	2020-03-05	Yes	151	mg/dL	0	150	.	Not Clinically Significant	

Listing 7.7 - Study IP-001-09 : Biochemistry - Triglycerides

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	187	mg/dL	0	150	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	154	mg/dL	0	150	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	171	mg/dL	0	150	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	155	mg/dL	0	150	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	205	mg/dL	0	150	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	177	mg/dL	0	150	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	244	mg/dL	0	150	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	217	mg/dL	0	150	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	151	mg/dL	0	150	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	203	mg/dL	0	150	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	108	mg/dL	0	150	.	Normal
	Day 0	2021-11-30	Yes	84	mg/dL	0	150	.	Normal
	Day 14	2021-12-14	Yes	108	mg/dL	0	150	.	Normal
	Day 28	2021-12-30	Yes	97	mg/dL	0	150	.	Normal
	Day 42	2022-01-15	Yes	104	mg/dL	0	150	.	Normal
	Day 56	2022-02-03	Yes	69	mg/dL	0	150	.	Normal
06-001	Screening	2021-12-15	Yes	65	mg/dL	20	170	.	Normal
06-002	Screening	2021-12-15	Yes	55	mg/dL	20	170	.	Not Clinically Significant

Listing 7.8 - Study IP-001-09 : Biochemistry - Total proteins

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	6.2	g/dl	6.3	8.2	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	6.3	g/dl	6.3	8.2	.	Normal
	Day 14	2019-11-28	Yes	6.6	g/dl	6.3	8.2	.	Normal
	Day 28	2019-12-12	Yes	5.9	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	6.4	md/dL	6.4	8.3	.	Normal
	Day 56	2020-01-07	Yes	6.1	md/dL	6.4	8.3	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	6.3	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-11	Yes	5.9	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	5.8	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	6.1	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	5.8	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	5.5	md/dL	6.4	8.3	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	6.0	g/dl	6.3	8.2	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	5.6	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	5.8	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	5.6	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	5.4	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	5.2	md/dL	6.4	8.3	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	6.4	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-13	Yes	5.9	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	6.3	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	6.5	mg/dL	6.4	8.3	.	Normal
	Day 42	2020-01-23	Yes	6.1	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	6.5	mg/dL	6.4	8.3	.	Normal
01-005	Screening	2019-11-15	Yes	7.5	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-13	Yes	6.5	md/dL	6.4	8.3	.	Normal
	Day 14	2019-12-27	Yes	6.5	md/dL	6.4	8.3	.	Normal
	Day 28	2020-01-10	Yes	6.7	md/dL	6.4	8.3	.	Normal
	Day 42	2020-01-24	Yes	7.1	md/dL	6.4	8.3	.	Normal
	Day 56	2020-02-07	Yes	6.7	md/dL	6.4	8.3	.	Normal
01-006	Screening	2019-11-20	Yes	7.1	g/dl	6.3	8.2	.	Normal

Listing 7.8 - Study IP-001-09 : Biochemistry - Total proteins

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	6.7	md/dL	6.4	8.3	.	Normal
	Day 14	2020-01-03	Yes	6.8	md/dL	6.4	8.3	.	Normal
	Day 28	2020-01-15	Yes	6.6	md/dL	6.4	8.3	.	Normal
	Day 42	2020-01-29	Yes	6.7	md/dL	6.4	8.3	.	Normal
	Day 56	2020-02-12	Yes	6.8	md/dL	6.4	8.3	.	Normal
01-007	Screening	2019-11-21	No	7.1	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-19	Yes	7.3	md/dL	6.4	8.3	.	Normal
	Day 14	2020-01-03	Yes	7.3	md/dL	6.4	8.3	.	Normal
	Day 28	2020-01-16	Yes	6.9	md/dL	6.4	8.3	.	Normal
	Day 42	2020-01-30	Yes	6.7	md/dL	6.4	8.3	.	Normal
	Day 56	2020-02-13	Yes	6.7	md/dL	6.4	8.3	.	Normal
01-008	Screening	2019-11-21	Yes	6.8	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-19	Yes	6.7	md/dL	6.4	8.3	.	Normal
	Day 14	2020-01-03	Yes	6.9	md/dL	6.4	8.3	.	Normal
	Day 28	2020-01-16	Yes	6.6	md/dL	6.4	8.3	.	Normal
	Day 42	2020-01-30	Yes	6.6	md/dL	6.4	8.3	.	Normal
	Day 56	2020-02-13	Yes	6.8	md/dL	6.4	8.3	.	Normal
01-009	Screening	2019-11-26	Yes	6.4	g/dl	6.3	8.2	.	Normal
	Day 0	2019-12-23	Yes	5.9	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	6.1	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	5.9	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	5.9	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	6.3	mg/dL	6.4	8.3	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	6.2	md/dL	6.4	8.3	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	6.5	md/dL	6.4	8.3	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	6.1	mg/dL	6.4	8.3	.	Not Clinically Significant
	Day 0	2020-03-05	Yes	6.9	mg/dL	6.4	8.3	.	Normal

Listing 7.8 - Study IP-001-09 : Biochemistry - Total proteins

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	6.6	mg/dL	6.4	8.3	.	Normal
	Day 28	2020-04-02	Yes	6.7	mg/dL	6.4	8.3	.	Normal
	Day 42	2020-04-16	Yes	6.6	mg/dL	6.4	8.3	.	Normal
	Day 56	2020-04-30	Yes	6.6	mg/dL	6.4	8.3	.	Normal
05-001	Screening	2021-10-13	No	5.7	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	5.5	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	5.6	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	5.4	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	5.5	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	5.8	g/dL	6.4	8.2	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	6.2	g/dL	6.4	8.2	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	6.6	g/dL	6.4	8.2	.	Normal
	Day 14	2021-12-14	Yes	6.5	g/dL	6.4	8.2	.	Normal
	Day 28	2021-12-30	Yes	6.5	g/dL	6.4	8.2	.	Normal
	Day 42	2022-01-15	Yes	7.1	g/dL	6.4	8.2	.	Normal
	Day 56	2022-02-03	Yes	6.3	g/dL	6.4	8.2	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	60.0	g/L	65.0	85.0	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	69.0	g/L	65.0	85.0	.	Not Clinically Significant

Listing 7.9 - Study IP-001-09 : Biochemistry - Albumin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 0	2019-11-13	Yes	3.50	g/dl	3.5	5.2	.	Normal
	Day 14	2019-11-28	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 28	2019-12-12	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 42	2019-12-23	Yes	4.00	g/dl	3.5	5.2	.	Normal
	Day 56	2020-01-07	Yes	3.90	g/dl	3.5	5.2	.	Normal
01-002	Screening	2019-11-13	Yes	3.93	g/dl	3.5	5.2	.	Normal
	Day 0	2019-12-11	Yes	3.74	g/dl	3.5	5.2	.	Normal
	Day 14	2019-12-27	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-08	Yes	4.00	g/dl	3.5	5.2	.	Normal
	Day 42	2020-01-22	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-05	Yes	3.70	g/dl	3.5	5.2	.	Normal
01-003	Screening	2019-11-13	Yes	3.81	g/dl	3.5	5.2	.	Normal
	Day 0	2019-12-11	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 14	2019-12-27	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-10	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 42	2020-01-22	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-05	Yes	3.50	g/dl	3.5	5.2	.	Normal
01-004	Screening	2019-11-15	Yes	3.85	g/dl	3.5	5.2	.	Normal
	Day 0	2019-12-13	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 14	2019-12-27	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-09	Yes	4.00	g/dl	3.5	5.2	.	Normal
	Day 42	2020-01-23	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-10	Yes	4.00	g/dl	3.5	5.2	.	Normal
01-005	Screening	2019-11-15	Yes	4.01	g/dl	3.5	5.2	.	Normal
	Day 0	2019-12-13	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 14	2019-12-27	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-10	Yes	0.25	g/dl	3.5	5.2	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	3.90	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-07	Yes	3.80	g/dl	3.5	5.2	.	Normal
01-006	Screening	2019-11-20	Yes	3.97	g/dl	3.5	5.2	.	Normal

Listing 7.9 - Study IP-001-09 : Biochemistry - Albumin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 14	2020-01-03	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-15	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 42	2020-01-29	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-12	Yes	3.90	g/dl	3.5	5.2	.	Normal
01-007	Screening	2019-11-21	No	4.09	g/dl	3.5	5.2	.	Normal
	Day 0	2019-12-19	Yes	4.00	g/dl	3.5	5.2	.	Normal
	Day 14	2020-01-03	Yes	4.00	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-16	Yes	4.00	g/dl	3.5	5.2	.	Normal
	Day 42	2020-01-30	Yes	4.00	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-13	Yes	3.60	g/dl	3.5	5.2	.	Normal
01-008	Screening	2019-11-21	Yes	4.34	g/dl	3.5	5.2	.	Normal
	Day 0	2019-12-19	Yes	4.10	g/dl	3.5	5.2	.	Normal
	Day 14	2020-01-03	Yes	4.10	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-16	Yes	4.10	g/dl	3.5	5.2	.	Normal
	Day 42	2020-01-30	Yes	4.20	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-13	Yes	4.00	g/dl	3.5	5.2	.	Normal
01-009	Screening	2019-11-26	Yes	2.51	g/dl	3.5	5.2	.	Not Clinically Significant
	Day 0	2019-12-23	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 14	2020-01-07	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 28	2020-01-21	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 42	2020-02-04	Yes	3.80	g/dl	3.5	5.2	.	Normal
	Day 56	2020-02-18	Yes	3.90	g/dl	3.5	5.2	.	Normal
01-010	Screening	2019-12-12	Yes	3.31	g/dl	3.5	5.2	.	Not Clinically Significant
	Day 0	2020-01-08	Yes	3.60	g/dl	3.5	5.2	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	3.50	g/dl	3.5	5.2	.	Normal
	Day 0	2020-03-05	Yes	3.90	g/dl	3.5	5.2	.	Normal

Listing 7.9 - Study IP-001-09 : Biochemistry - Albumin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 28	2020-04-02	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 42	2020-04-16	Yes	3.70	g/dl	3.5	5.2	.	Normal
	Day 56	2020-04-30	Yes	3.80	g/dl	3.5	5.2	.	Normal
05-001	Screening	2021-10-13	No	2.40	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	2.00	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	2.40	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	2.20	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	2.50	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	2.50	g/dL	3.4	5.0	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	3.10	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	3.20	g/dL	3.4	5.0	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	3.60	g/dL	3.4	5.0	.	Normal
	Day 28	2021-12-30	Yes	3.40	g/dL	3.4	5.0	.	Normal
	Day 42	2022-01-15	Yes	3.70	g/dL	3.4	5.0	.	Normal
	Day 56	2022-02-03	Yes	3.00	g/dL	3.4	5.0	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	31.00	g/L	34.0	48.0	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	41.00	g/L	34.0	48.0	.	Not Clinically Significant

Listing 7.10 - Study IP-001-09 : Biochemistry - Total bilirubin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done		Evaluation	
01-001	Screening	2019-10-16	Yes	.	mg/dl	0.2	1.3	Yes			.
	Day 0	2019-11-13	Yes	0.86	mg/dl	0.2	1.3	.	Normal		
	Day 14	2019-11-28	Yes	0.77	mg/dl	0.2	1.3	.	Normal		
	Day 28	2019-12-12	Yes	.	mg/dL	0.2	1.2	Yes			.
	Day 42	2019-12-23	Yes	0.83	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-01-07	Yes	0.74	mg/dL	0.2	1.2	.	Normal		
01-002	Screening	2019-11-13	Yes	0.60	mg/dl	0.2	1.3	.	Normal		
	Day 0	2019-12-11	Yes	.	mg/dL	0.2	1.2	Yes			.
	Day 14	2019-12-27	Yes	0.62	mg/dL	0.2	1.2	.	Normal		
	Day 28	2020-01-08	Yes	0.82	mg/dL	0.2	1.2	.	Normal		
	Day 42	2020-01-22	Yes	0.47	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-02-05	Yes	0.44	mg/dL	0.2	1.2	.	Normal		
01-003	Screening	2019-11-13	Yes	0.55	mg/dl	0.2	1.3	.	Normal		
	Day 0	2019-12-11	Yes	0.50	mg/dL	0.2	1.2	.	Normal		
	Day 14	2019-12-27	Yes	0.50	mg/dL	0.2	1.2	.	Normal		
	Day 28	2020-01-10	Yes	0.49	mg/dL	0.2	1.2	.	Normal		
	Day 42	2020-01-22	Yes	0.55	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-02-05	Yes	0.43	mg/dL	0.2	1.2	.	Normal		
01-004	Screening	2019-11-15	Yes	0.43	mg/dl	0.2	1.3	.	Normal		
	Day 0	2019-12-13	Yes	0.36	mg/dL	0.2	1.2	.	Normal		
	Day 14	2019-12-27	Yes	0.49	mg/dL	0.2	1.2	.	Normal		
	Day 28	2020-01-09	Yes	0.32	mg/dL	0.2	1.2	.	Normal		
	Day 42	2020-01-23	Yes	0.41	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-02-10	Yes	0.38	mg/dL	0.2	1.2	.	Normal		
01-005	Screening	2019-11-15	Yes	0.46	mg/dl	0.2	1.3	.	Normal		
	Day 0	2019-12-13	Yes	0.35	mg/dL	0.2	1.2	.	Normal		
	Day 14	2019-12-27	Yes	0.44	mg/dL	0.2	1.2	.	Normal		
	Day 28	2020-01-10	Yes	0.25	mg/dL	0.2	1.2	.	Normal		
	Day 42	2020-01-24	Yes	0.27	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-02-07	Yes	0.24	mg/dL	0.2	1.2	.	Normal		
01-006	Screening	2019-11-20	Yes	0.61	mg/dl	0.2	1.3	.	Normal		

Listing 7.10 - Study IP-001-09 : Biochemistry - Total bilirubin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	0.50	mg/dL	0.2	1.2	.	Normal	
	Day 14	2020-01-03	Yes	0.71	mg/dL	0.2	1.2	.	Normal	
	Day 28	2020-01-15	Yes	0.35	mg/dL	0.2	1.2	.	Normal	
	Day 42	2020-01-29	Yes	0.53	mg/dL	0.2	1.2	.	Normal	
	Day 56	2020-02-12	Yes	0.50	mg/dL	0.2	1.2	.	Normal	
01-007	Screening	2019-11-21	No	0.54	mg/dl	0.2	1.3	.	Normal	
	Day 0	2019-12-19	Yes	0.37	mg/dL	0.2	1.2	.	Normal	
	Day 14	2020-01-03	Yes	0.37	mg/dL	0.2	1.2	.	Normal	
	Day 28	2020-01-16	Yes	0.30	mg/dL	0.2	1.2	.	Normal	
	Day 42	2020-01-30	Yes	0.36	mg/dL	0.2	1.2	.	Normal	
	Day 56	2020-02-13	Yes	0.36	mg/dL	0.2	1.2	.	Normal	
01-008	Screening	2019-11-21	Yes	0.96	mg/dl	0.2	1.3	.	Normal	
	Day 0	2019-12-19	Yes	0.77	mg/dL	0.2	1.2	.	Normal	
	Day 14	2020-01-03	Yes	0.75	mg/dL	0.2	1.2	.	Normal	
	Day 28	2020-01-16	Yes	0.70	mg/dL	0.2	1.2	.	Normal	
	Day 42	2020-01-30	Yes	0.65	mg/dL	0.2	1.2	.	Normal	
	Day 56	2020-02-13	Yes	0.64	mg/dL	0.2	1.2	.	Normal	
01-009	Screening	2019-11-26	Yes	0.62	mg/dl	0.2	1.3	.	Normal	
	Day 0	2019-12-23	Yes	0.61	mg/dL	0.2	1.2	.	Normal	
	Day 14	2020-01-07	Yes	0.66	mg/dL	0.2	1.2	.	Normal	
	Day 28	2020-01-21	Yes	0.53	mg/dL	0.2	1.2	.	Normal	
	Day 42	2020-02-04	Yes	0.55	mg/dL	0.2	1.2	.	Normal	
	Day 56	2020-02-18	Yes	0.49	mg/dL	0.2	1.2	.	Normal	
01-010	Screening	2019-12-12	Yes	0.33	mg/dL	0.2	1.2	.	Normal	
	Day 0	2020-01-08	Yes	0.43	mg/dL	0.2	1.2	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	0.47	mg/dL	0.2	1.2	.	Normal	
	Day 0	2020-03-05	Yes	0.55	mg/dL	0.2	1.2	.	Normal	

Listing 7.10 - Study IP-001-09 : Biochemistry - Total bilirubin

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done		Evaluation	
01-011	Day 14	2020-03-20	Yes	0.52	mg/dL	0.2	1.2	.	Normal		
	Day 28	2020-04-02	Yes	0.57	mg/dL	0.2	1.2	.	Normal		
	Day 42	2020-04-16	Yes	0.57	mg/dL	0.2	1.2	.	Normal		
	Day 56	2020-04-30	Yes	0.44	mg/dL	0.2	1.2	.	Normal		
05-001	Screening	2021-10-13	No	0.32	mg/dL	0.2	1.0	.	Normal		
	Day 0	2021-11-10	Yes	0.30	mg/dL	0.2	1.0	.	Normal		
	Day 14	2021-11-26	Yes	0.30	mg/dL	0.2	1.0	.	Normal		
	Day 28	2021-12-09	Yes	0.20	mg/dL	0.2	1.0	.	Normal		
	Day 42	2022-01-28	Yes	0.25	mg/dL	0.2	1.0	.	Normal		
	Day 56	2022-02-22	Yes	.	mg/dL	0.2	1.0	Yes			.
05-002	Screening	2021-10-29	Yes	0.30	mg/dL	0.2	1.0	.	Normal		
	Day 0	2021-11-30	Yes	.	mg/dL	0.2	1.0	Yes			.
	Day 14	2021-12-14	Yes	0.30	mg/dL	0.2	1.0	.	Normal		
	Day 28	2021-12-30	Yes	0.31	mg/dL	0.2	1.0	.	Normal		
	Day 42	2022-01-15	Yes	0.34	mg/dL	0.2	1.0	.	Normal		
	Day 56	2022-02-03	Yes	0.30	mg/dL	0.2	1.0	.	Normal		
06-001	Screening	2021-12-15	Yes	.	mg/dl	0.3	1.2	Yes			.
06-002	Screening	2021-12-15	Yes	.	mg/dl	0.3	1.2	Yes			.

Listing 7.11 - Study IP-001-09 : Biochemistry - SGOT (AST)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	15	U/L	15	46	.	Normal
	Day 0	2019-11-13	Yes	20	U/L	15	46	.	Normal
	Day 14	2019-11-28	Yes	20	U/L	15	46	.	Normal
	Day 28	2019-12-12	Yes	14	U/L	5	34	.	Normal
	Day 42	2019-12-23	Yes	13	U/L	5	34	.	Normal
	Day 56	2020-01-07	Yes	11	U/L	5	34	.	Normal
01-002	Screening	2019-11-13	Yes	18	U/L	15	46	.	Normal
	Day 0	2019-12-11	Yes	15	U/L	5	34	.	Normal
	Day 14	2019-12-27	Yes	15	U/L	5	34	.	Normal
	Day 28	2020-01-08	Yes	12	U/L	5	34	.	Normal
	Day 42	2020-01-22	Yes	17	U/L	5	34	.	Normal
	Day 56	2020-02-05	Yes	12	U/L	5	34	.	Normal
01-003	Screening	2019-11-13	Yes	14	U/L	15	46	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	8	U/L	5	34	.	Normal
	Day 14	2019-12-27	Yes	9	U/L	5	34	.	Normal
	Day 28	2020-01-10	Yes	7	U/L	5	34	.	Normal
	Day 42	2020-01-22	Yes	9	U/L	5	34	.	Normal
	Day 56	2020-02-05	Yes	9	U/L	5	34	.	Normal
01-004	Screening	2019-11-15	Yes	21	U/L	14	36	.	Normal
	Day 0	2019-12-13	Yes	10	U/L	5	34	.	Normal
	Day 14	2019-12-27	Yes	11	U/L	5	34	.	Normal
	Day 28	2020-01-09	Yes	10	U/L	5	34	.	Normal
	Day 42	2020-01-23	Yes	10	U/L	5	34	.	Normal
	Day 56	2020-02-10	Yes	13	U/L	5	34	.	Normal
01-005	Screening	2019-11-15	Yes	17	U/L	15	46	.	Normal
	Day 0	2019-12-13	Yes	7	U/L	5	34	.	Normal
	Day 14	2019-12-27	Yes	11	U/L	5	34	.	Normal
	Day 28	2020-01-10	Yes	8	U/L	5	34	.	Normal
	Day 42	2020-01-24	Yes	9	U/L	5	34	.	Normal
	Day 56	2020-02-07	Yes	8	U/L	5	34	.	Normal
01-006	Screening	2019-11-20	Yes	22	U/L	15	46	.	Normal

Listing 7.11 - Study IP-001-09 : Biochemistry - SGOT (AST)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	10	U/L	5	34	.	Normal	
	Day 14	2020-01-03	Yes	19	U/L	5	34	.	Normal	
	Day 28	2020-01-15	Yes	22	U/L	5	34	.	Normal	
	Day 42	2020-01-29	Yes	16	U/L	5	34	.	Normal	
	Day 56	2020-02-12	Yes	13	U/L	5	34	.	Normal	
01-007	Screening	2019-11-21	No	18	U/L	15	46	.	Normal	
	Day 0	2019-12-19	Yes	15	U/L	5	34	.	Normal	
	Day 14	2020-01-03	Yes	13	U/L	5	34	.	Normal	
	Day 28	2020-01-16	Yes	10	U/L	5	34	.	Normal	
	Day 42	2020-01-30	Yes	10	U/L	5	34	.	Normal	
	Day 56	2020-02-13	Yes	7	U/L	5	34	.	Normal	
01-008	Screening	2019-11-21	Yes	32	U/L	15	46	.	Normal	
	Day 0	2019-12-19	Yes	18	U/L	5	34	.	Normal	
	Day 14	2020-01-03	Yes	18	U/L	5	34	.	Normal	
	Day 28	2020-01-16	Yes	21	U/L	5	34	.	Normal	
	Day 42	2020-01-30	Yes	18	U/L	5	34	.	Normal	
	Day 56	2020-02-13	Yes	13	U/L	5	34	.	Normal	
01-009	Screening	2019-11-26	Yes	19	U/L	14	36	.	Normal	
	Day 0	2019-12-23	Yes	14	U/L	5	34	.	Normal	
	Day 14	2020-01-07	Yes	14	U/L	5	34	.	Normal	
	Day 28	2020-01-21	Yes	15	U/L	5	34	.	Normal	
	Day 42	2020-02-04	Yes	16	U/L	5	34	.	Normal	
	Day 56	2020-02-18	Yes	16	U/L	5	34	.	Normal	
01-010	Screening	2019-12-12	Yes	16	U/L	5	34	.	Normal	
	Day 0	2020-01-08	Yes	17	U/L	5	34	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	13	U/L	5	34	.	Normal	
	Day 0	2020-03-05	Yes	15	U/L	5	34	.	Normal	

Listing 7.11 - Study IP-001-09 : Biochemistry - SGOT (AST)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-011	Day 14	2020-03-20	Yes	13	U/L	5	34	.	Normal	
	Day 28	2020-04-02	Yes	15	U/L	5	34	.	Normal	
	Day 42	2020-04-16	Yes	18	U/L	5	34	.	Normal	
	Day 56	2020-04-30	Yes	15	U/L	5	34	.	Normal	
05-001	Screening	2021-10-13	No	15	U/L	15	37	.	Normal	
	Day 0	2021-11-10	Yes	12	U/L	15	37	.	Not Clinically Significant	
	Day 14	2021-11-26	Yes	15	U/L	15	37	.	Normal	
	Day 28	2021-12-09	Yes	16	U/L	15	37	.	Normal	
	Day 42	2022-01-28	Yes	12	U/L	15	37	.	Not Clinically Significant	
	Day 56	2022-02-22	Yes	.	U/L	15	37	Yes		.
05-002	Screening	2021-10-29	Yes	14	U/L	15	37	.	Not Clinically Significant	
	Day 0	2021-11-30	Yes	.	U/L	15	37	Yes		.
	Day 14	2021-12-14	Yes	17	U/L	15	37	.	Normal	
	Day 28	2021-12-30	Yes	17	U/L	15	37	.	Normal	
	Day 42	2022-01-15	Yes	21	U/L	15	37	.	Normal	
	Day 56	2022-02-03	Yes	21	U/L	15	37	.	Normal	
06-001	Screening	2021-12-15	Yes	8	UI/L	7	45	.	Normal	
06-002	Screening	2021-12-15	Yes	13	UI/L	7	45	.	Not Clinically Significant	

Listing 7.12 - Study IP-001-09 : Biochemistry - SGPT (ALT)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	17	U/L	11	66	.	Normal
	Day 0	2019-11-13	Yes	16	U/L	11	66	.	Normal
	Day 14	2019-11-28	Yes	23	U/L	11	66	.	Normal
	Day 28	2019-12-12	Yes	15	U/L	0	55	.	Normal
	Day 42	2019-12-23	Yes	16	U/L	0	55	.	Normal
	Day 56	2020-01-07	Yes	16	U/L	0	55	.	Normal
01-002	Screening	2019-11-13	Yes	17	U/L	11	66	.	Normal
	Day 0	2019-12-11	Yes	16	U/L	0	55	.	Normal
	Day 14	2019-12-27	Yes	18	U/L	0	55	.	Normal
	Day 28	2020-01-08	Yes	13	U/L	0	55	.	Normal
	Day 42	2020-01-22	Yes	18	U/L	0	55	.	Normal
	Day 56	2020-02-05	Yes	14	U/L	0	55	.	Normal
01-003	Screening	2019-11-13	Yes	10	U/L	11	66	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	9	U/L	0	55	.	Normal
	Day 14	2019-12-27	Yes	9	U/L	0	55	.	Normal
	Day 28	2020-01-10	Yes	7	U/L	0	55	.	Normal
	Day 42	2020-01-22	Yes	9	U/L	0	55	.	Normal
	Day 56	2020-02-05	Yes	10	U/L	0	55	.	Normal
01-004	Screening	2019-11-15	Yes	18	U/L	9	52	.	Normal
	Day 0	2019-12-13	Yes	13	U/L	0	55	.	Normal
	Day 14	2019-12-27	Yes	13	U/L	0	55	.	Normal
	Day 28	2020-01-09	Yes	18	U/L	0	55	.	Normal
	Day 42	2020-01-23	Yes	14	U/L	0	55	.	Normal
	Day 56	2020-02-10	Yes	16	U/L	0	55	.	Normal
01-005	Screening	2019-11-15	Yes	16	U/L	11	66	.	Normal
	Day 0	2019-12-13	Yes	12	U/L	0	55	.	Normal
	Day 14	2019-12-27	Yes	18	U/L	0	55	.	Normal
	Day 28	2020-01-10	Yes	12	U/L	0	55	.	Normal
	Day 42	2020-01-24	Yes	14	U/L	0	55	.	Normal
	Day 56	2020-02-07	Yes	13	U/L	0	55	.	Normal
01-006	Screening	2019-11-20	Yes	21	U/L	11	66	.	Normal

Listing 7.12 - Study IP-001-09 : Biochemistry - SGPT (ALT)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	14	U/L	0	55	.	Normal	
	Day 14	2020-01-03	Yes	28	U/L	0	55	.	Normal	
	Day 28	2020-01-15	Yes	40	U/L	0	55	.	Normal	
	Day 42	2020-01-29	Yes	28	U/L	0	55	.	Normal	
	Day 56	2020-02-12	Yes	19	U/L	0	55	.	Normal	
01-007	Screening	2019-11-21	No	12	U/L	11	66	.	Normal	
	Day 0	2019-12-19	Yes	17	U/L	0	55	.	Normal	
	Day 14	2020-01-03	Yes	17	U/L	0	55	.	Normal	
	Day 28	2020-01-16	Yes	11	U/L	0	55	.	Normal	
	Day 42	2020-01-30	Yes	13	U/L	0	55	.	Normal	
	Day 56	2020-02-13	Yes	15	U/L	0	55	.	Normal	
01-008	Screening	2019-11-21	Yes	35	U/L	11	66	.	Normal	
	Day 0	2019-12-19	Yes	27	U/L	0	55	.	Normal	
	Day 14	2020-01-03	Yes	35	U/L	0	55	.	Normal	
	Day 28	2020-01-16	Yes	34	U/L	0	55	.	Normal	
	Day 42	2020-01-30	Yes	32	U/L	0	55	.	Normal	
	Day 56	2020-02-13	Yes	19	U/L	0	55	.	Normal	
01-009	Screening	2019-11-26	Yes	12	U/L	9	52	.	Normal	
	Day 0	2019-12-23	Yes	11	U/L	0	55	.	Normal	
	Day 14	2020-01-07	Yes	10	U/L	0	55	.	Normal	
	Day 28	2020-01-21	Yes	11	U/L	0	55	.	Normal	
	Day 42	2020-02-04	Yes	13	U/L	0	55	.	Normal	
	Day 56	2020-02-18	Yes	12	U/L	0	55	.	Normal	
01-010	Screening	2019-12-12	Yes	13	U/L	0	55	.	Normal	
	Day 0	2020-01-08	Yes	24	U/L	0	55	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	8	U/L	0	55	.	Normal	
	Day 0	2020-03-05	Yes	9	U/L	0	55	.	Normal	

Listing 7.12 - Study IP-001-09 : Biochemistry - SGPT (ALT)

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-011	Day 14	2020-03-20	Yes	8	U/L	0	55	.	Normal	
	Day 28	2020-04-02	Yes	7	U/L	0	55	.	Normal	
	Day 42	2020-04-16	Yes	10	U/L	0	55	.	Normal	
	Day 56	2020-04-30	Yes	9	U/L	0	55	.	Normal	
05-001	Screening	2021-10-13	No	17	U/L	12	78	.	Normal	
	Day 0	2021-11-10	Yes	11	U/L	12	78	.	Not Clinically Significant	
	Day 14	2021-11-26	Yes	14	U/L	12	78	.	Normal	
	Day 28	2021-12-09	Yes	18	U/L	12	78	.	Normal	
	Day 42	2022-01-28	Yes	16	U/L	12	78	.	Normal	
	Day 56	2022-02-22	Yes	.	U/L	12	78	Yes		.
05-002	Screening	2021-10-29	Yes	18	U/L	12	78	.	Normal	
	Day 0	2021-11-30	Yes	.	U/L	12	78	Yes		.
	Day 14	2021-12-14	Yes	54	U/L	12	78	.	Normal	
	Day 28	2021-12-30	Yes	31	U/L	12	78	.	Normal	
	Day 42	2022-01-15	Yes	29	U/L	12	78	.	Normal	
	Day 56	2022-02-03	Yes	43	U/L	12	78	.	Normal	
06-001	Screening	2021-12-15	Yes	12	UI/L	7	45	.	Normal	
06-002	Screening	2021-12-15	Yes	20	UI/L	7	45	.	Not Clinically Significant	

Listing 7.13 - Study IP-001-09 : Biochemistry - Alkaline Phosphatase

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-001	Screening	2019-10-16	Yes	80	U/L	38	126	.	Normal	
	Day 0	2019-11-13	Yes	82	U/L	38	126	.	Normal	
	Day 14	2019-11-28	Yes	92	U/L	38	126	.	Normal	
	Day 28	2019-12-12	Yes	102	U/L	40	150	.	Normal	
	Day 42	2019-12-23	Yes	115	U/L	40	150	.	Normal	
	Day 56	2020-01-07	Yes	114	U/L	40	150	.	Normal	
01-002	Screening	2019-11-13	Yes	61	U/L	38	126	.	Normal	
	Day 0	2019-12-11	Yes	64	U/L	40	150	.	Normal	
	Day 14	2019-12-27	Yes	73	U/L	40	150	.	Normal	
	Day 28	2020-01-08	Yes	69	U/L	40	150	.	Normal	
	Day 42	2020-01-22	Yes	65	U/L	40	150	.	Normal	
	Day 56	2020-02-05	Yes	66	U/L	40	150	.	Normal	
01-003	Screening	2019-11-13	Yes	120	U/L	38	126	.	Normal	
	Day 0	2019-12-11	Yes	167	U/L	40	150	.	Not Clinically Significant	
	Day 14	2019-12-27	Yes	.	U/L	40	150	Yes		.
	Day 28	2020-01-10	Yes	185	U/L	40	150	.	Not Clinically Significant	
	Day 42	2020-01-22	Yes	164	U/L	40	150	.	Not Clinically Significant	
	Day 56	2020-02-05	Yes	196	U/L	40	150	.	Not Clinically Significant	
01-004	Screening	2019-11-15	Yes	50	U/L	38	126	.	Normal	
	Day 0	2019-12-13	Yes	67	U/L	40	150	.	Normal	
	Day 14	2019-12-27	Yes	63	U/L	40	150	.	Normal	
	Day 28	2020-01-09	Yes	64	U/L	40	150	.	Normal	
	Day 42	2020-01-23	Yes	59	U/L	40	150	.	Normal	
	Day 56	2020-02-10	Yes	63	U/L	40	150	.	Normal	
01-005	Screening	2019-11-15	Yes	52	U/L	38	126	.	Normal	
	Day 0	2019-12-13	Yes	56	U/L	40	150	.	Normal	
	Day 14	2019-12-27	Yes	.	U/L	40	150	Yes		.
	Day 28	2020-01-10	Yes	58	U/L	40	150	.	Normal	
	Day 42	2020-01-24	Yes	68	U/L	40	150	.	Normal	
	Day 56	2020-02-07	Yes	62	U/L	40	150	.	Normal	
01-006	Screening	2019-11-20	Yes	53	U/L	38	126	.	Normal	

Listing 7.13 - Study IP-001-09 : Biochemistry - Alkaline Phosphatase

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-006	Day 0	2019-12-18	Yes	53	U/L	40	150	.	Normal	
	Day 14	2020-01-03	Yes	54	U/L	40	150	.	Normal	
	Day 28	2020-01-15	Yes	.	U/L	40	150	Yes		.
	Day 42	2020-01-29	Yes	55	U/L	40	150	.	Normal	
	Day 56	2020-02-12	Yes	53	U/L	40	150	.	Normal	
01-007	Screening	2019-11-21	No	72	U/L	38	126	.	Normal	
	Day 0	2019-12-19	Yes	73	U/L	40	150	.	Normal	
	Day 14	2020-01-03	Yes	64	U/L	40	150	.	Normal	
	Day 28	2020-01-16	Yes	67	U/L	40	150	.	Normal	
	Day 42	2020-01-30	Yes	64	U/L	40	150	.	Normal	
	Day 56	2020-02-13	Yes	75	U/L	40	150	.	Normal	
01-008	Screening	2019-11-21	Yes	61	U/L	38	126	.	Normal	
	Day 0	2019-12-19	Yes	76	U/L	40	150	.	Normal	
	Day 14	2020-01-03	Yes	111	U/L	40	150	.	Normal	
	Day 28	2020-01-16	Yes	86	U/L	40	150	.	Normal	
	Day 42	2020-01-30	Yes	95	U/L	40	150	.	Normal	
	Day 56	2020-02-13	Yes	84	U/L	40	150	.	Normal	
01-009	Screening	2019-11-26	Yes	82	U/L	38	126	.	Normal	
	Day 0	2019-12-23	Yes	94	U/L	40	150	.	Normal	
	Day 14	2020-01-07	Yes	85	U/L	40	150	.	Normal	
	Day 28	2020-01-21	Yes	91	U/L	40	150	.	Normal	
	Day 42	2020-02-04	Yes	93	U/L	40	150	.	Normal	
	Day 56	2020-02-18	Yes	102	U/L	40	150	.	Normal	
01-010	Screening	2019-12-12	Yes	85	U/L	40	150	.	Normal	
	Day 0	2020-01-08	Yes	112	U/L	40	150	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	47	U/L	40	150	.	Normal	
	Day 0	2020-03-05	Yes	54	U/L	40	150	.	Normal	

Listing 7.13 - Study IP-001-09 : Biochemistry - Alkaline Phosphatase

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	38	U/L	40	150	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	43	U/L	40	150	.	Normal
	Day 42	2020-04-16	Yes	38	U/L	40	150	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	44	U/L	40	150	.	Normal
05-001	Screening	2021-10-13	No	163	U/L	43	115	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	114	U/L	43	115	.	Normal
	Day 14	2021-11-26	Yes	161	U/L	43	115	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	147	U/L	43	115	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	153	U/L	43	115	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	.	U/L	43	115	Yes	.
05-002	Screening	2021-10-29	Yes	141	U/L	43	115	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	.	U/L	43	115	Yes	.
	Day 14	2021-12-14	Yes	115	U/L	43	115	.	Normal
	Day 28	2021-12-30	Yes	132	U/L	43	115	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	171	U/L	43	115	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	159	U/L	43	115	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	151	UI/L	40	129	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	72	UI/L	40	129	.	Not Clinically Significant

Listing 7.14 - Study IP-001-09 : Biochemistry - GGT

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	14	U/L	15	73	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	16	U/L	15	73	.	Normal
	Day 14	2019-11-28	Yes	23	U/L	15	73	.	Normal
	Day 28	2019-12-12	Yes	18	U/L	12	64	.	Normal
	Day 42	2019-12-23	Yes	16	U/L	12	64	.	Normal
	Day 56	2020-01-07	Yes	13	U/L	12	64	.	Normal
01-002	Screening	2019-11-13	Yes	15	U/L	15	73	.	Normal
	Day 0	2019-12-11	Yes	15	U/L	12	64	.	Normal
	Day 14	2019-12-27	Yes	15	U/L	12	64	.	Normal
	Day 28	2020-01-08	Yes	16	U/L	12	64	.	Normal
	Day 42	2020-01-22	Yes	17	U/L	12	64	.	Normal
	Day 56	2020-02-05	Yes	14	U/L	12	64	.	Normal
01-003	Screening	2019-11-13	Yes	13	U/L	15	73	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	14	U/L	12	64	.	Normal
	Day 14	2019-12-27	Yes	14	U/L	12	64	.	Normal
	Day 28	2020-01-10	Yes	185	U/L	12	64	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	12	U/L	12	64	.	Normal
	Day 56	2020-02-05	Yes	12	U/L	12	64	.	Normal
01-004	Screening	2019-11-15	Yes	10	U/L	12	43	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	10	U/L	9	36	.	Normal
	Day 14	2019-12-27	Yes	11	U/L	9	36	.	Normal
	Day 28	2020-01-09	Yes	14	U/L	9	36	.	Normal
	Day 42	2020-01-23	Yes	13	U/L	9	36	.	Normal
	Day 56	2020-02-10	Yes	12	U/L	9	36	.	Normal
01-005	Screening	2019-11-15	Yes	31	U/L	15	73	.	Normal
	Day 0	2019-12-13	Yes	33	U/L	12	64	.	Normal
	Day 14	2019-12-27	Yes	38	U/L	12	64	.	Normal
	Day 28	2020-01-10	Yes	43	U/L	12	64	.	Normal
	Day 42	2020-01-24	Yes	39	U/L	12	64	.	Normal
	Day 56	2020-02-07	Yes	34	U/L	12	64	.	Normal
01-006	Screening	2019-11-20	Yes	66	U/L	15	73	.	Normal

Listing 7.14 - Study IP-001-09 : Biochemistry - GGT

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done		Evaluation
01-006	Day 0	2019-12-18	Yes	44	U/L	12	64	.	Normal	
	Day 14	2020-01-03	Yes	55	U/L	12	64	.	Normal	
	Day 28	2020-01-15	Yes	58	U/L	12	64	.	Normal	
	Day 42	2020-01-29	Yes	57	U/L	12	64	.	Normal	
	Day 56	2020-02-12	Yes	55	U/L	12	64	.	Normal	
01-007	Screening	2019-11-21	No	29	U/L	15	73	.	Normal	
	Day 0	2019-12-19	Yes	27	U/L	12	64	.	Normal	
	Day 14	2020-01-03	Yes	27	U/L	12	64	.	Normal	
	Day 28	2020-01-16	Yes	21	U/L	12	64	.	Normal	
	Day 42	2020-01-30	Yes	21	U/L	12	64	.	Normal	
	Day 56	2020-02-13	Yes	27	U/L	12	64	.	Normal	
01-008	Screening	2019-11-21	Yes	21	U/L	15	73	.	Normal	
	Day 0	2019-12-19	Yes	18	U/L	12	64	.	Normal	
	Day 14	2020-01-03	Yes	26	U/L	12	64	.	Normal	
	Day 28	2020-01-16	Yes	28	U/L	12	64	.	Normal	
	Day 42	2020-01-30	Yes	24	U/L	12	64	.	Normal	
	Day 56	2020-02-13	Yes	23	U/L	12	64	.	Normal	
01-009	Screening	2019-11-26	Yes	19	U/L	12	43	.	Normal	
	Day 0	2019-12-23	Yes	16	U/L	9	36	.	Normal	
	Day 14	2020-01-07	Yes	18	U/L	9	36	.	Normal	
	Day 28	2020-01-21	Yes	17	U/L	9	36	.	Normal	
	Day 42	2020-02-04	Yes	17	U/L	9	36	.	Normal	
	Day 56	2020-02-18	Yes	18	U/L	9	36	.	Normal	
01-010	Screening	2019-12-12	Yes	19	U/L	12	64	.	Normal	
	Day 0	2020-01-08	Yes	25	U/L	12	64	.	Normal	
	Day 14			.		.	.	.		.
	Day 28			.		.	.	.		.
	Day 42			.		.	.	.		.
	Day 56			.		.	.	.		.
01-011	Screening	2020-02-06	Yes	10	U/L	9	36	.	Normal	
	Day 0	2020-03-05	Yes	11	U/L	9	36	.	Normal	

Listing 7.14 - Study IP-001-09 : Biochemistry - GGT

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation	
01-011	Day 14	2020-03-20	Yes	10	U/L	9	36	.	Normal	
	Day 28	2020-04-02	Yes	11	U/L	9	36	.	Normal	
	Day 42	2020-04-16	Yes	69	U/L	9	36	.	Not Clinically Significant	
	Day 56	2020-04-30	Yes	13	U/L	9	36	.	Normal	
05-001	Screening	2021-10-13	No	14	U/L	15	85	.	Not Clinically Significant	
	Day 0	2021-11-10	Yes	12	U/L	15	85	.	Not Clinically Significant	
	Day 14	2021-11-26	Yes	19	U/L	15	85	.	Normal	
	Day 28	2021-12-09	Yes	17	U/L	15	85	.	Normal	
	Day 42	2022-01-28	Yes	13	U/L	15	85	.	Not Clinically Significant	
	Day 56	2022-02-22	Yes	.	U/L	15	85	Yes		.
05-002	Screening	2021-10-29	Yes	74	U/L	15	85	.	Normal	
	Day 0	2021-11-30	Yes	.	U/L	15	85	Yes		.
	Day 14	2021-12-14	Yes	55	U/L	15	85	.	Normal	
	Day 28	2021-12-30	Yes	66	U/L	15	85	.	Normal	
	Day 42	2022-01-15	Yes	96	U/L	15	85	.	Not Clinically Significant	
	Day 56	2022-02-03	Yes	80	U/L	15	85	.	Normal	
06-001	Screening	2021-12-15	Yes	15	UI/L	8	61	.	Normal	
06-002	Screening	2021-12-15	Yes	8	UI/L	8	61	.	Not Clinically Significant	

Listing 7.15 - Study IP-001-09 : Biochemistry - Serum Sodium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	137.0	mmol/L	136	146	.	Normal
	Day 0	2019-11-13	Yes	143.0	mmol/L	136	146	.	Normal
	Day 14	2019-11-28	Yes	140.0	mmol/L	136	146	.	Normal
	Day 28	2019-12-12	Yes	140.0	mmol/L	136	146	.	Normal
	Day 42	2019-12-23	Yes	140.0	mmol/L	136	146	.	Normal
	Day 56	2020-01-07	Yes	141.0	mmol/L	136	146	.	Normal
01-002	Screening	2019-11-13	Yes	137.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-11	Yes	138.0	mmol/L	136	146	.	Normal
	Day 14	2019-12-27	Yes	136.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-08	Yes	136.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-22	Yes	137.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-05	Yes	135.0	mmol/L	136	146	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	138.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-11	Yes	140.0	mmol/L	136	146	.	Normal
	Day 14	2019-12-27	Yes	137.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-10	Yes	137.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-22	Yes	137.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-05	Yes	140.0	mmol/L	136	146	.	Normal
01-004	Screening	2019-11-15	Yes	136.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-13	Yes	138.0	mmol/L	136	146	.	Normal
	Day 14	2019-12-27	Yes	136.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-09	Yes	135.0	mmol/L	136	146	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	137.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-10	Yes	137.0	mmol/L	136	146	.	Normal
01-005	Screening	2019-11-15	Yes	137.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-13	Yes	136.0	mmol/L	136	146	.	Normal
	Day 14	2019-12-27	Yes	139.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-10	Yes	136.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-24	Yes	134.0	mmol/L	136	146	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	136.0	mmol/L	136	146	.	Normal
01-006	Screening	2019-11-20	Yes	143.0	mmol/L	136	146	.	Normal

Listing 7.15 - Study IP-001-09 : Biochemistry - Serum Sodium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	141.0	mmol/L	136	146	.	Normal
	Day 14	2020-01-03	Yes	145.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-15	Yes	143.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-29	Yes	145.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-12	Yes	141.0	mmol/L	136	146	.	Normal
01-007	Screening	2019-11-21	No	136.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-19	Yes	138.0	mmol/L	136	146	.	Normal
	Day 14	2020-01-03	Yes	138.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-16	Yes	139.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-30	Yes	135.0	mmol/L	136	146	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	136.0	mmol/L	136	146	.	Normal
01-008	Screening	2019-11-21	Yes	142.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-19	Yes	141.0	mmol/L	136	146	.	Normal
	Day 14	2020-01-03	Yes	141.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-16	Yes	142.0	mmol/L	136	146	.	Normal
	Day 42	2020-01-30	Yes	139.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-13	Yes	138.0	mmol/L	136	146	.	Normal
01-009	Screening	2019-11-26	Yes	140.0	mmol/L	136	146	.	Normal
	Day 0	2019-12-23	Yes	135.0	mmol/L	136	146	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	138.0	mmol/L	136	146	.	Normal
	Day 28	2020-01-21	Yes	135.0	mmol/L	136	146	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	137.0	mmol/L	136	146	.	Normal
	Day 56	2020-02-18	Yes	136.0	mmol/L	136	146	.	Normal
01-010	Screening	2019-12-12	Yes	140.0	mmol/L	136	146	.	Normal
	Day 0	2020-01-08	Yes	140.0	mmol/L	136	146	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	142.0	mmol/L	136	146	.	Normal
	Day 0	2020-03-05	Yes	138.0	mmol/L	136	146	.	Normal

Listing 7.15 - Study IP-001-09 : Biochemistry - Serum Sodium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	140.0	mmol/L	136	146	.	Normal
	Day 28	2020-04-02	Yes	140.0	mmol/L	136	146	.	Normal
	Day 42	2020-04-16	Yes	144.0	mmol/L	136	146	.	Normal
	Day 56	2020-04-30	Yes	3.8	mmol/L	136	146	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	139.0	mEq/L	136	145	.	Normal
	Day 0	2021-11-10	Yes	130.0	mEq/L	136	145	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	135.0	mEq/L	136	145	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	139.0	mEq/L	136	145	.	Normal
	Day 42	2022-01-28	Yes	133.0	mEq/L	136	145	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	133.0	mEq/L	136	145	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	132.0	mEq/L	136	145	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	131.0	mEq/L	136	145	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	133.0	mEq/L	136	145	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	133.0	mEq/L	136	145	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	132.0	mEq/L	136	145	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	131.0	mEq/L	136	145	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	137.0	mmol/L	135	145	.	Normal
06-002	Screening	2021-12-15	Yes	143.0	mmol/L	135	145	.	Not Clinically Significant

Listing 7.16 - Study IP-001-09 : Biochemistry - Potassium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	5.45	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	5.37	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	5.55	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	5.50	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	5.50	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	5.30	mmol/L	3.5	5.1	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	5.37	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	4.40	mmol/L	3.5	5.1	.	Normal
	Day 14	2019-12-27	Yes	4.70	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-01-08	Yes	4.50	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-22	Yes	5.20	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	4.10	mmol/L	3.5	5.1	.	Normal
01-003	Screening	2019-11-13	Yes	4.18	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-11	Yes	4.20	mmol/L	3.5	5.1	.	Normal
	Day 14	2019-12-27	Yes	3.90	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-01-10	Yes	3.80	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-22	Yes	4.30	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-02-05	Yes	4.60	mmol/L	3.5	5.1	.	Normal
01-004	Screening	2019-11-15	Yes	5.03	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-13	Yes	4.90	mmol/L	3.5	5.1	.	Normal
	Day 14	2019-12-27	Yes	5.10	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-01-09	Yes	5.00	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-23	Yes	5.20	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	5.00	mmol/L	3.5	5.1	.	Normal
01-005	Screening	2019-11-15	Yes	4.99	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-13	Yes	4.50	mmol/L	3.5	5.1	.	Normal
	Day 14	2019-12-27	Yes	4.30	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-01-10	Yes	4.30	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-24	Yes	4.50	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-02-07	Yes	4.60	mmol/L	3.5	5.1	.	Normal
01-006	Screening	2019-11-20	Yes	3.52	mmol/L	3.5	5.1	.	Normal

Listing 7.16 - Study IP-001-09 : Biochemistry - Potassium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	3.40	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	3.30	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	3.30	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	3.50	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-02-12	Yes	3.50	mmol/L	3.5	5.1	.	Normal
01-007	Screening	2019-11-21	No	4.77	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-19	Yes	4.60	mmol/L	3.5	5.1	.	Normal
	Day 14	2020-01-03	Yes	5.30	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	4.60	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-30	Yes	5.30	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	5.20	mmol/L	3.5	5.1	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	4.72	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-19	Yes	5.00	mmol/L	3.5	5.1	.	Normal
	Day 14	2020-01-03	Yes	4.60	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-01-16	Yes	4.80	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-01-30	Yes	4.80	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-02-13	Yes	4.30	mmol/L	3.5	5.1	.	Normal
01-009	Screening	2019-11-26	Yes	4.73	mmol/L	3.5	5.1	.	Normal
	Day 0	2019-12-23	Yes	5.20	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	5.30	mmol/L	3.5	5.1	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	4.70	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-02-04	Yes	4.90	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-02-18	Yes	4.60	mmol/L	3.5	5.1	.	Normal
01-010	Screening	2019-12-12	Yes	4.70	mmol/L	3.5	5.1	.	Normal
	Day 0	2020-01-08	Yes	4.50	mmol/L	3.5	5.1	.	Normal
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	4.90	mmol/L	3.5	5.1	.	Normal
	Day 0	2020-03-05	Yes	4.90	mmol/L	3.5	5.1	.	Normal

Listing 7.16 - Study IP-001-09 : Biochemistry - Potassium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	4.60	mmol/L	3.5	5.1	.	Normal
	Day 28	2020-04-02	Yes	4.30	mmol/L	3.5	5.1	.	Normal
	Day 42	2020-04-16	Yes	4.50	mmol/L	3.5	5.1	.	Normal
	Day 56	2020-04-30	Yes	3.70	mmol/L	3.5	5.1	.	Normal
05-001	Screening	2021-10-13	No	4.50	mEq/L	3.5	5.0	.	Normal
	Day 0	2021-11-10	Yes	3.50	mEq/L	3.5	5.0	.	Normal
	Day 14	2021-11-26	Yes	5.60	mEq/L	3.5	5.0	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	4.50	mEq/L	3.5	5.0	.	Normal
	Day 42	2022-01-28	Yes	4.50	mEq/L	3.5	5.0	.	Normal
	Day 56	2022-02-22	Yes	4.60	mEq/L	3.5	5.0	.	Normal
05-002	Screening	2021-10-29	Yes	4.00	mEq/L	3.5	5.0	.	Normal
	Day 0	2021-11-30	Yes	4.90	mEq/L	3.5	5.0	.	Normal
	Day 14	2021-12-14	Yes	3.90	mEq/L	3.5	5.0	.	Normal
	Day 28	2021-12-30	Yes	3.90	mEq/L	3.5	5.0	.	Normal
	Day 42	2022-01-15	Yes	3.80	mEq/L	3.5	5.0	.	Normal
	Day 56	2022-02-03	Yes	3.80	mEq/L	3.5	5.0	.	Normal
06-001	Screening	2021-12-15	Yes	3.90	mmol/L	3.5	5.0	.	Normal
06-002	Screening	2021-12-15	Yes	4.40	mmol/L	3.5	5.0	.	Not Clinically Significant

Listing 7.17 - Study IP-001-09 : Biochemistry - Calcium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	2.4	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-11-13	Yes	2.4	mmol/L	2.1	2.55	.	Normal
	Day 14	2019-11-28	Yes	2.4	mmol/L	2.1	2.55	.	Normal
	Day 28	2019-12-12	Yes	8.9	mg/dL	8.8	10.20	.	Normal
	Day 42	2019-12-23	Yes	9.4	mg/dL	8.8	10.20	.	Normal
	Day 56	2020-01-07	Yes	9.2	mg/dL	8.8	10.20	.	Normal
01-002	Screening	2019-11-13	Yes	2.2	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-11	Yes	8.9	mg/dL	8.8	10.20	.	Normal
	Day 14	2019-12-27	Yes	8.4	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	9.3	mg/dL	8.8	10.20	.	Normal
	Day 42	2020-01-22	Yes	8.5	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	8.7	mg/dL	8.8	10.20	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	2.2	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-11	Yes	8.8	mg/dL	8.8	10.20	.	Normal
	Day 14	2019-12-27	Yes	8.3	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	8.5	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	8.5	mg/dL	8.8	10.20	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	2.3	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-13	Yes	8.9	mg/dL	8.8	10.20	.	Normal
	Day 14	2019-12-27	Yes	9.0	mg/dL	8.8	10.20	.	Normal
	Day 28	2020-01-09	Yes	9.2	mg/dL	8.8	10.20	.	Normal
	Day 42	2020-01-23	Yes	9.0	mg/dL	8.8	10.20	.	Normal
	Day 56	2020-02-10	Yes	8.9	mg/dL	8.8	10.20	.	Normal
01-005	Screening	2019-11-15	Yes	2.2	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-13	Yes	9.1	mg/dL	8.8	10.20	.	Normal
	Day 14	2019-12-27	Yes	9.5	mg/dL	8.8	10.20	.	Normal
	Day 28	2020-01-10	Yes	9.6	mg/dL	8.8	10.20	.	Normal
	Day 42	2020-01-24	Yes	9.6	mg/dL	8.8	10.20	.	Normal
	Day 56	2020-02-07	Yes	9.0	mg/dL	8.8	10.20	.	Normal
01-006	Screening	2019-11-20	Yes	2.2	mmol/L	2.1	2.55	.	Normal

Listing 7.17 - Study IP-001-09 : Biochemistry - Calcium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	8.4	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	8.4	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 42	2020-01-29	Yes	8.5	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-12	Yes	8.8	mg/dL	8.8	10.20	.	Normal
01-007	Screening	2019-11-21	No	2.4	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-19	Yes	11.9	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	8.7	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	8.0	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	8.4	mg/dL	8.8	10.20	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	2.5	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-19	Yes	10.0	mg/dL	8.8	10.20	.	Normal
	Day 14	2020-01-03	Yes	9.4	mg/dL	8.8	10.20	.	Normal
	Day 28	2020-01-16	Yes	10.5	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	10.5	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	2.3	mmol/L	2.1	2.55	.	Normal
	Day 0	2019-12-23	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	9.2	mg/dL	8.8	10.20	.	Normal
	Day 28	2020-01-21	Yes	8.4	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	8.7	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	8.5	mg/dL	8.8	10.20	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	7.6	mg/dL	8.8	10.20	.	Clinically sign. for the pathology under study
	Day 0	2020-01-08	Yes	7.9	mg/dL	8.8	10.20	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	9.2	mg/dL	8.8	10.20	.	Normal
	Day 0	2020-03-05	Yes	9.8	mg/dL	8.8	10.20	.	Normal

Listing 7.17 - Study IP-001-09 : Biochemistry - Calcium

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	9.5	mg/dL	8.8	10.20	.	Normal
	Day 28	2020-04-02	Yes	9.7	mg/dL	8.8	10.20	.	Normal
	Day 42	2020-04-16	Yes	10.1	mg/dL	8.8	10.20	.	Normal
	Day 56	2020-04-30	Yes	8.6	mg/dL	8.8	10.20	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	7.7	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 0	2021-11-10	Yes	7.3	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 14	2021-11-26	Yes	8.3	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 28	2021-12-09	Yes	7.8	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 42	2022-01-28	Yes	8.0	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	9.0	mg/dL	8.5	10.10	.	Normal
05-002	Screening	2021-10-29	Yes	8.5	mg/dL	8.5	10.10	.	Normal
	Day 0	2021-11-30	Yes	8.2	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	8.3	mg/dL	8.5	10.10	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	8.6	mg/dL	8.5	10.10	.	Normal
	Day 42	2022-01-15	Yes	8.7	mg/dL	8.5	10.10	.	Normal
	Day 56	2022-02-03	Yes	8.3	mg/dL	8.5	10.10	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	8.7	mg/dL	8.6	10.20	.	Normal
06-002	Screening	2021-12-15	Yes	9.9	mg/dL	8.6	10.20	.	Not Clinically Significant

Listing 7.18 - Study IP-001-09 : Biochemistry - Phosphorus

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-001	Screening	2019-10-16	Yes	1.90	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-11-13	Yes	1.70	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 14	2019-11-28	Yes	1.80	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 28	2019-12-12	Yes	5.80	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2019-12-23	Yes	5.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-01-07	Yes	5.70	mg/dL	2.30	4.30	.	Not Clinically Significant
01-002	Screening	2019-11-13	Yes	1.60	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-12-11	Yes	4.60	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	5.70	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-08	Yes	4.50	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	4.90	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	4.60	mg/dL	2.30	4.30	.	Not Clinically Significant
01-003	Screening	2019-11-13	Yes	0.81	mmol/L	0.81	1.45	.	Clinically significant for concomitant disease
	Day 0	2019-12-11	Yes	6.60	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	6.70	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	6.60	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-22	Yes	6.40	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-05	Yes	6.50	mg/dL	2.30	4.30	.	Not Clinically Significant
01-004	Screening	2019-11-15	Yes	2.20	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	5.70	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	7.10	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-09	Yes	5.70	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-23	Yes	6.40	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-10	Yes	6.50	mg/dL	2.30	4.30	.	Not Clinically Significant
01-005	Screening	2019-11-15	Yes	1.80	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-12-13	Yes	6.20	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2019-12-27	Yes	5.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-10	Yes	5.10	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-24	Yes	5.50	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-07	Yes	5.40	mg/dL	2.30	4.30	.	Not Clinically Significant
01-006	Screening	2019-11-20	Yes	1.40	mmol/L	0.81	1.45	.	Normal

Listing 7.18 - Study IP-001-09 : Biochemistry - Phosphorus

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-006	Day 0	2019-12-18	Yes	4.10	mg/dL	2.30	4.30	.	Normal
	Day 14	2020-01-03	Yes	4.50	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-15	Yes	3.40	mg/dL	2.30	4.30	.	Normal
	Day 42	2020-01-29	Yes	4.00	mg/dL	2.30	4.30	.	Normal
	Day 56	2020-02-12	Yes	4.50	mg/dL	2.30	4.30	.	Not Clinically Significant
01-007	Screening	2019-11-21	No	2.10	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	6.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	7.00	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-16	Yes	7.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	6.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-13	Yes	6.40	mg/dL	2.30	4.30	.	Not Clinically Significant
01-008	Screening	2019-11-21	Yes	1.80	mmol/L	0.81	1.45	.	Not Clinically Significant
	Day 0	2019-12-19	Yes	4.60	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2020-01-03	Yes	3.20	mg/dL	2.30	4.30	.	Normal
	Day 28	2020-01-16	Yes	5.40	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-01-30	Yes	3.80	mg/dL	2.30	4.30	.	Normal
	Day 56	2020-02-13	Yes	5.40	mg/dL	2.30	4.30	.	Not Clinically Significant
01-009	Screening	2019-11-26	Yes	1.60	mmol/L	0.81	1.45	.	Clinically sign. for the pathology under study
	Day 0	2019-12-23	Yes	4.60	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14	2020-01-07	Yes	4.90	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-01-21	Yes	4.90	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-02-04	Yes	4.80	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-02-18	Yes	4.50	mg/dL	2.30	4.30	.	Not Clinically Significant
01-010	Screening	2019-12-12	Yes	5.40	mg/dL	2.30	4.30	.	Clinically sign. for the pathology under study
	Day 0	2020-01-08	Yes	5.70	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 14			.		.	.	.	.
	Day 28			.		.	.	.	.
	Day 42			.		.	.	.	.
	Day 56			.		.	.	.	.
01-011	Screening	2020-02-06	Yes	5.40	mg/dL	2.30	4.30	.	Clinically sign. for the pathology under study
	Day 0	2020-03-05	Yes	5.20	mg/dL	2.30	4.30	.	Not Clinically Significant

Listing 7.18 - Study IP-001-09 : Biochemistry - Phosphorus

Patient no.	Visit no.	Sample collection date (yy-mm-dd)	Patient fasting	Result	Unit	Normal range -Low-	Normal range -High-	Test not done	Evaluation
01-011	Day 14	2020-03-20	Yes	4.80	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 28	2020-04-02	Yes	4.90	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 42	2020-04-16	Yes	6.30	mg/dL	2.30	4.30	.	Not Clinically Significant
	Day 56	2020-04-30	Yes	5.10	mg/dL	2.30	4.30	.	Not Clinically Significant
05-001	Screening	2021-10-13	No	4.00	mg/dL	2.50	4.90	.	Normal
	Day 0	2021-11-10	Yes	4.40	mg/dL	2.50	4.90	.	Normal
	Day 14	2021-11-26	Yes	3.90	mg/dL	2.50	4.90	.	Normal
	Day 28	2021-12-09	Yes	3.70	mg/dL	2.50	4.90	.	Normal
	Day 42	2022-01-28	Yes	5.60	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 56	2022-02-22	Yes	6.30	mg/dL	2.50	4.90	.	Not Clinically Significant
05-002	Screening	2021-10-29	Yes	7.00	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 0	2021-11-30	Yes	6.00	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 14	2021-12-14	Yes	5.40	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 28	2021-12-30	Yes	6.30	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 42	2022-01-15	Yes	6.10	mg/dL	2.50	4.90	.	Not Clinically Significant
	Day 56	2022-02-03	Yes	5.80	mg/dL	2.50	4.90	.	Not Clinically Significant
06-001	Screening	2021-12-15	Yes	4.80	mg/dL	2.50	4.50	.	Not Clinically Significant
06-002	Screening	2021-12-15	Yes	4.30	mg/dL	2.50	4.50	.	Not Clinically Significant

Listing 8 - Study IP-001-09 : Weekly Total Urea Kt/v, Peritoneal Equilibration Test (PET) and Weekly total Creatinine Clearance

Patient no.	Visit no.	Weekly Total urea Kt/v	PET Dialysate/ Plasma creatinine	Weekly Total Creatinine Clearance
01-001	Day 0	0.76	0.66	61.46
	Day 28	1.52	0.74	69.88
	Day 56	1.58	0.70	70.98
01-002	Day 0	1.59	0.59	86.94
	Day 28	1.75	0.64	98.15
	Day 56	1.56	0.68	80.70
01-003	Day 0	1.45	0.61	72.22
	Day 28	1.54	0.67	65.83
	Day 56	1.35	0.70	68.22
01-004	Day 0	1.24	0.61	50.03
	Day 28	1.08	0.66	42.38
	Day 56	1.14	0.51	42.60
01-005	Day 0	1.10	0.22	78.04
	Day 28	1.07	0.72	55.45
	Day 56	1.06	0.70	59.66
01-006	Day 0	1.68	0.62	93.39
	Day 28	1.70	0.63	105.74
	Day 56	1.49	0.57	91.53
01-007	Day 0	1.52	0.57	77.76
	Day 28	1.57	0.60	79.55
	Day 56	1.14	0.62	58.06
01-008	Day 0	1.36	0.53	62.62
	Day 28	1.47	0.56	65.56
	Day 56	1.35	0.53	62.31
01-009	Day 0	1.43	0.57	85.52

Listing 8 - Study IP-001-09 : Weekly Total Urea Kt/v, Peritoneal Equilibration Test (PET) and Weekly total Creatinine Clearance

Patient no.	Visit no.	Weekly Total urea Kt/v	PET Dialysate/ Plasma creatinine	Weekly Total Creatinine Clearance
01-009	Day 28	1.42	0.59	95.78
	Day 56	1.84	0.57	112.38
01-010	Day 0	0.95	0.63	50.70
	Day 28	.	.	.
	Day 56	.	.	.
01-011	Day 0	1.12	0.48	55.46
	Day 28	1.42	0.61	80.25
	Day 56	1.49	0.53	65.26
05-001	Day 0	1.20	0.71	53.87
	Day 28	1.29	0.71	51.85
	Day 56	.	.	.
05-002	Day 0	1.23	0.71	43.28
	Day 28	1.12	0.59	42.69
	Day 56	1.12	0.62	42.83

Listing 9 - Study IP-001-09 : Subjective questionnaire

Patient no.	Visit no.	Questionnaire filled	Questionnaire Total score
01-001	Day 0	Yes	15
	Day 28	Yes	15
	Day 56	Yes	15
01-002	Day 0	Yes	15
	Day 28	Yes	15
	Day 56	Yes	15
01-003	Day 0	Yes	17
	Day 28	Yes	20
	Day 56	Yes	23
01-004	Day 0	Yes	14
	Day 28	Yes	19
	Day 56	Yes	16
01-005	Day 0	Yes	25
	Day 28	Yes	18
	Day 56	Yes	18
01-006	Day 0	Yes	22
	Day 28	Yes	18
	Day 56	Yes	15
01-007	Day 0	Yes	17
	Day 28	Yes	21
	Day 56	Yes	19
01-008	Day 0	Yes	17
	Day 28	Yes	16
	Day 56	Yes	15
01-009	Day 0	Yes	16
	Day 28	Yes	17
	Day 56	Yes	15

Listing 9 - Study IP-001-09 : Subjective questionnaire

Patient no.	Visit no.	Questionnaire filled	Questionnaire Total score
01-010	Day 0	Yes	17
	Day 28		.
	Day 56		.
01-011	Day 0	Yes	19
	Day 28	Yes	17
	Day 56	Yes	16
05-001	Day 0	Yes	20
	Day 28	Yes	26
	Day 56	No	.
05-002	Day 0	Yes	21
	Day 28	Yes	25
	Day 56	Yes	24

Listing 10 - Study IP-001-09 : ECG - evaluation

Patient no.	Visit no.	ECG normal	ECG abnormality	ECG evaluation
01-001	Day 0	No	Sinus Bradycardia	Clinically significant for concomitant disease
	Day 28	No	Sinus Bradycardia	Clinically sign. for the pathology under study
01-002	Day 0	Yes	.	.
	Day 28	Yes	.	.
01-003	Day 0	Yes	.	.
	Day 28	Yes	.	.
01-004	Day 0	Yes	.	.
	Day 28	Yes	.	.
01-005	Day 0	No	Sinus Bradycardia	Clinically significant for concomitant disease
	Day 28	Yes	.	.
01-006	Day 0	No	Sinus Bradycardia	Clinically significant for concomitant disease
	Day 28	No	Right Bundle Branch Block	Clinically significant for concomitant disease
01-007	Day 0	No	Left Bundle Branch Block	Clinically significant for concomitant disease
	Day 28	No	Left Bundle Branch Block	Clinically significant for concomitant disease
01-008	Day 0	Yes	.	.
	Day 28	Yes	.	.
01-009	Day 0	No	Other: Sinus rhythm, previous lower myocardial infarction	Clinically significant for concomitant disease
	Day 28	Yes	.	.
01-010	Day 0	Yes	.	.
01-011	Day 0	Yes	.	.
	Day 28	Yes	.	.

Listing 10 - Study IP-001-09 : ECG - evaluation

Patient no.	Visit no.	ECG normal	ECG abnormality	ECG evaluation
05-001	Day 0	Yes	.	.
	Day 28	Yes	.	.
05-002	Day 0	Yes	.	.
	Day 28	Yes	.	.

Listing 11 - Study IP-001-09 : Adverse events (AE)

Patient no.	AE num.	Event	Start date (yy-mm-dd)	End date (yy-mm-dd)	Seriousness	Intensity	Relation to study drug	Action taken	Outcome
01-002	1	Turbid peritoneal fluid	2019-12-27		Not serious	Mild	Not related	None	Not recovered
01-003	1	Anemia	2019-12-11		Not serious	Mild	Not related	Specific therapy/medication	Not recovered
01-004	1	Hyperphosphataemia	2019-12-27		Not serious	Mild	Not related	None	Not recovered
05-001	1	Macroglossia	2021-12-09		Not serious	Mild	Unlikely related	None	Not recovered
	2	insomnia	2021-12-05		Not serious	Mild	Not related	None	Not recovered
	3	Dispnea	2021-12-18		Not serious	Mild	Unlikely related	Specific therapy/medication	Not recovered
05-002	1	itching	2021-11-04		Not serious	Mild	Not related	None	Not recovered
	2	swollen legs	2021-12-19		Not serious	Mild	Unlikely related	None	Not recovered
	3	mild bilateral legs edema	2022-02-03		Not serious	Mild	Unlikely related	None	Not recovered

Listing 12 - Study IP-001-09 : Previous and Concomitant medications (CM)

Patient no.	Medication	Start date (dd/mm/yy)	End date (dd/mm/yy)	Ongoing	Total dose	Unit	Frequency	Route	Indication
01-001	Atenololo	13/12/2019		Yes	50.00	mg	QD	PO	Hypertension
	lasix	na/na/2015		Yes	50.00	mg	BID	PO	hypertension
	goltor	na/na/2017		Yes	.	mg	QD	PO	hypercholesterolemia
	rocaltrol	na/na/2019		Yes	.	mcg	QD	PO	CKD-MBD
	coral	na/na/2017		Yes	30.00	mg	QD	PO	hypertension
	esomeprazolo	na/na/2015		Yes	20.00	mg	QD	PO	GERD
	Atenololo	na/na/2015	12/12/2019	No	100.00	mg	QD	PO	hypertension
	zyloric	na/na/2017		Yes	300.00	mg	QD	PO	hyperuricemia
	renagel	na/04/2019		Yes	3200.00	mg	BID	PO	CKD-MBD
	olpress	na/na/2015		Yes	20.00	mg	QD	PO	hypertension
01-002	Zyloric	na/na/2018		Yes	300.00	mg	ONCE	PO	Hyperuricemia
	rocaltrol	na/05/2019		Yes	.	mcg	ONCE	PO	CKD-MBD
	diuresix	na/na/2010		Yes	10.00	mg	ONCE	PO	hypertension
	vytorin	na/na/2015		Yes	.	mg	ONCE	PO	hypercholesterolemia
	cardura	na/na/2010		Yes	4.00	mg	ONCE	PO	hypertension
	Tenormin	na/na/2007		Yes	25.00	mg	ONCE	PO	Post infarct heart disease
	cacit	na/05/2019		Yes	2000.00	mg	BID	PO	CKD-MBD
	lantus	na/na/2013		Yes	12.00	UI	ONCE	SC	diabetes mellitus
	apidra	na/na/2013		Yes	30.00	UI	TID	SC	diabetes mellitus
	plavix	na/na/2015		Yes	75.00	mg	ONCE	PO	secondary prevention
01-003	zyloric	na/na/2018		Yes	300.00	mg	ONCE	PO	hyperuricemia
	xatral	na/na/2005		Yes	10.00	mg	ONCE	PO	Benign prostatic hypertrophy
	mimpara	na/08/2019		Yes	30.00	mg	ONCE	PO	CKD-MBD
	renagel	na/06/2019		Yes	7200.00	mg	TID	PO	CKD-MBD
	binocrit	20/12/2019		Yes	6000.00	UI	OTH	SC	secondary anemia
01-004	lasix	na/na/2014		Yes	50.00	mg	BID	PO	hypertension
	dilatrend	na/na/2014		Yes	.	mg	BID	PO	hypertension
	binocrit	na/09/2019		Yes	6000.00	UI	OTH	SC	secondary anemia
	adalat crono	na/na/2019		Yes	30.00	mg	ONCE	PO	hypertension
	renagel	na/06/2019	27/12/2019	No	1600.00	mg	ONCE	PO	CKD-MBD
	maalox	27/12/2019		Yes	1.00	spoon	BID	PO	hyperphosphataemia
	rocaltrol	na/06/2019		Yes	.	mcg	ONCE	PO	CKD-MBD
	goltor	na/na/2017		Yes	.	mg	ONCE	PO	hypercholesterolemia
	zyloric	na/06/2019		Yes	150.00	mg	ONCE	PO	hyperuricemia
	omeprazolo	na/na/2015		Yes	10.00	mg	ONCE	PO	GERD
01-005	repaglinide	na/na/2010		Yes	2.00	mg	BID	PO	diebetes mellitus
	cardura	na/na/2010		Yes	4.00	mg	ONCE	PO	hypertension

Listing 12 - Study IP-001-09 : Previous and Concomitant medications (CM)

Patient no.	Medication	Start date (dd/mm/yy)	End date (dd/mm/yy)	Ongoing	Total dose	Unit	Frequency	Route	Indication
01-005	adalat crono	na/na/2010		Yes	120.00	mg	BID	PO	hypertension
	rocaltrol	na/06/2019		Yes	0.25	mcg	ONCE	PO	CKD-MBD
	eskim	na/na/2003		Yes	2000.00	mg	BID	PO	dyslipidemia
	retacrit	na/08/2019		Yes	4000.00	UI	OTH	SC	secondary anemia
	lasix	na/na/2018		Yes	250.00	mg	BID	PO	hypertension
	congescor	na/na/2010		Yes	2.50	mg	ONCE	PO	hypertension
	zyloric	na/na/2017		Yes	150.00	mg	ONCE	PO	hyperuricemia
	cacit	na/06/2019		Yes	2000.00	mg	BID	PO	CKD-MBD
01-006	Nebivololo	na/na/2018		Yes	.	mg	QD	PO	Hypertension
	Binocrit	na/na/2019		Yes	4000.00	UI	OTH	SC	Secondary anemia
	Lansoprazolo	na/na/2015		Yes	15.00	mg	QD	PO	Gastroprotective
	Cardioaspirina	na/na/2010		Yes	100.00	mg	QD	PO	Antiplatelet
	Rocaltrol	na/na/2018		Yes	.	mcg	QD	PO	CKB-MBD
	Lasix	na/na/2018		Yes	250.00	mg	QD	PO	Hypertension
	Cardura	na/na/2015		Yes	8.00	mg	QD	PO	Hypertension
	Adenuric	na/na/2019		Yes	160.00	mg	OTH	PO	Hyperuricemia
	Eutirox	na/na/2005		Yes	100.00	mcg	QD	PO	Hypothyroidism
01-007	Cardioaspirina	na/na/2015		Yes	100.00	mg	QD	PO	Heart attack prevention
	Amlodipina	na/na/2015		Yes	10.00	mg	QD	PO	Hypertension
	Adenuric	na/na/2015		Yes	80.00	mg	QD	PO	Hyperuricemia
	Alprazolam	na/na/2010		Yes	1.00	mg	QD	PO	Anxious syndrome
	Renagel	20/12/2019		Yes	3200.00	mg	QD	PO	CKD-MBD
	Lasix	na/na/2015		Yes	25.00	mg	QD	PO	Hypertension
	Rocaltrol	na/na/2017		Yes	.	mcg	QD	PO	CKD-MBD
	Sequacor	na/na/2015		Yes	.	mg	QD	PO	Prevention heart attack
	Omega 3	na/na/2015		Yes	3000.00	mg	QD	PO	Dyslipidemia
	Atorvastatina	na/na/2015		Yes	20.00	mg	QD	PO	Dyslipidemia
	Binocrit	na/na/2015		Yes	6000.00	UI	OTH	SC	Anemia
	Zirtec	03/01/2020		Yes	10.00	mg	QD	PO	Chronic Kidney Disease- associated pruritus (CKD- aP)
01-008	zyloric	16/01/2020		Yes	150.00	1/2 cp	ONCE	PO	hyperuricemia
	Cacit	na/na/2019		Yes	2000.00	mg	QD	PO	CKD-MBD
	Vytorin	na/na/2005		Yes	.	mg	QD	PO	Prevention heart attack
	Binocrit	na/na/2019		Yes	6000.00	UI	OTH	SC	Secondary anemia
	Lasix	na/na/2018		Yes	75.00	mg	QD	PO	Hypertension
	Cardioaspirina	na/na/2005		Yes	100.00	mg	QD	PO	Prevention heart attack
	Rocaltrol	na/na/2019		Yes	.	mcg	QD	PO	CKD-MBD
	Lansoprazolo	na/na/2005		Yes	15.00	mg	QD	PO	Gastroprotective
	Amlodipina	na/na/2018		Yes	10.00	mg	QD	PO	Hypertension

Listing 12 - Study IP-001-09 : Previous and Concomitant medications (CM)

Patient no.	Medication	Start date (dd/mm/yy)	End date (dd/mm/yy)	Ongoing	Total dose	Unit	Frequency	Route	Indication
01-009	Eutirox	na/na/2012		Yes	75.00	mcg	OTH	PO	Hypothyroidism
	Cacit	na/na/2019		Yes	2000.00	mg	QD	PO	CKD-MBD
	Cardura	na/na/2017		Yes	8.00	mg	QD	PO	Hypertension
	Mimpara	na/na/2019		Yes	30.00	mg	QD	PO	CKD-MBD
	Lasix	na/na/2017		Yes	50.00	mg	QD	PO	Hypertension
	Eutirox	na/na/2012		Yes	50.00	mcg	OTH	PO	Hypothyroidism
	Peptazol	na/na/2017		Yes	20.00	mg	QD	PO	Gastritis type B
	Dilatrend	na/na/2017		Yes	.	mg	QD	PO	Hypertension
	Mircera	na/na/2019		Yes	75.00	mcg	OTH	SC	Secondary anemia
01-010	Cardura	na/na/2010		Yes	4.00	mg	QD	PO	Hypertension
	Congescor	na/na/2010		Yes	2.50	mg	QD	PO	Hypertension
	Zyloric	na/na/2017		Yes	150.00	mg	QD	PO	Hyperuricemia
	Cacit	na/na/2019		Yes	2000.00	mg	QD	PO	CKB-MBD
	Lasix	na/na/2010		Yes	125.00	mg	QD	PO	Hypertension
	Renagel	na/na/2019		Yes	4000.00	mg	QD	PO	CKB-MBD
	Rocaltrol	na/na/2019		Yes	0.25	mcg	QD	PO	CKB-MBD
	Binocrit	na/na/2019		Yes	6000.00	UI	OTH	SC	Secondary anemia
01-011	Adenuric	na/na/2017		Yes	80.00	mg	OTH	PO	Hyperuricemia
	Renagel	na/na/2019		Yes	1600.00	mg	QD	PO	CKB-MBD
	Nexium	na/na/2017		Yes	20.00	mg	QD	PO	Gastroprotective
	Rocaltrol	na/na/2019		Yes	0.25	mcg	QD	PO	CKB-MBD
	Binocrit	na/na/2019		Yes	6000.00	UI	OTH	SC	Secondary anemia
	Lasix	na/na/2010		Yes	50.00	mg	QD	PO	Hypertension
05-001	Zyloric	na/na/na		Yes	150.00	mg	ONCE	PO	CKD related hyperuricemia
	Coumadin	na/na/na		Yes	5.00	mg	PRN	PO	Atrial Fibrillation
	Antra	na/na/na		Yes	20.00	mg	ONCE	PO	prevention of gastroesophageal reflux
	Norvasc	na/na/na		Yes	5.00	mg	QD	PO	hypertension
	Omnic	na/na/na		Yes	0.40	mg	QD	PO	prostatic hypertrophy
	Rocaltrol	na/na/na		Yes	0.25	mg	QD	PO	CKD related hyperphosphorus
	Kayexalate	na/na/na		Yes	1.00	mis	PRN	PO	CKD related hyperkalaemia
	Totalip	na/na/na		Yes	10.00	mg	QD	PO	hypercholesterolemia
	Sodio Bicarbonato	na/na/na		Yes	1000.00	mg	ONCE	PO	prevention of CKD related acidosis
	Retacrit	na/na/na		Yes	4000.00	UI	OTH	IM	CKD related Anemia
	Normix	10/11/2021		Yes	200.00	mg	QD	PO	prevention of colitis
	Carbonate-Calcium	na/na/na		Yes	2000.00	mg	QID	PO	CKD related hypocalcemia
	Lasix	na/na/na		Yes	250.00	mg	BID	PO	hypertension
05-002	ESKIM	na/na/na		Yes	1000.00	mg	QD	PO	CKD related dyslipidemia

Listing 12 - Study IP-001-09 : Previous and Concomitant medications (CM)

Patient no.	Medication	Start date (dd/mm/yy)	End date (dd/mm/yy)	Ongoing	Total dose	Unit	Frequency	Route	Indication
05-002	NORVASC	na/na/na		Yes	10.00	mg	BID	PO	Hypertension
	Sevelamer	na/na/na	04/11/2021	No	7.20	g	TID	PO	CKD related Hyperfosforus
	DEURSIL	na/na/na		Yes	450.00	mg	QD	PO	biliary lithiasis prevention
	ROCALTROL	27/08/2021		Yes	0.25	MG	QD	PO	CKD related VIT.D shortage
	LANTUS	na/na/na		Yes	5.00	UI	PRN	IM	diabetes
	Cardioasa	na/na/na		Yes	100.00	mg	QD	PO	primary prevention
	Provisacor	na/na/na		Yes	20.00	mg	QD	PO	CKD related dyslipidemia
	RETACRIT	na/na/na		Yes	6000.00	UI	OTH	IM	CKD related anemia
	LASIX	na/na/na		Yes	250.00	MG	BID	PO	CKD
	ferrograd	21/09/2021	04/11/2021	No	105.00	mg	QD	PO	CKD related anemia
	HUMALOG	na/na/na	na/na/na	No	10.00	UI	PRN	IM	diabetes
06-001	renvela	na/na/na		Yes	800.00	mg	TID	PO	hyperphosphatemia
	zemplar	na/na/na		Yes	1.00	mcg	OTH	PO	hyperparathyroidism
	mircera	na/na/na		Yes	150.00	mcg	OTH	SC	anemia
	congescor	na/na/na		Yes	1.25	mg	QD	PO	hypertension
	cardura	na/na/na		Yes	4.00	mcg	QD	PO	hypertension
	lasix	na/na/na		Yes	50.00	mg	TID	PO	diuresis stimolation
	zemplar	na/na/na		Yes	2.00	mcg	OTH	PO	hyperparathyroidism
	mimpara	na/na/na		Yes	30.00	mg	QD	PO	hyperparathyroidism
	zyloric	na/na/na		Yes	100.00	mg	QD	PO	hyperuricemia
	norvasc	na/na/na		Yes	5.00	mg	QD	PO	hypertension
06-002	aranesp	na/na/na		Yes	40.00	mcg	OTH	SC	anemia
	lasix	na/na/na		Yes	75.00	mg	BID	PO	Diuresis stimolation
	loortan	na/na/na		Yes	100.00	mg	QD	PO	hypertension
	renvela	na/na/na		Yes	2.40	g	BID	PO	hyperphosphatemia
	rocaltrol	na/na/na		Yes	0.25	mcg	QD	PO	vitamin D deficiency
	ferinject	na/na/na		Yes	500.00	mg	OTH	IV	iron deficiency
	torvast	na/na/na		Yes	20.00	mg	QD	PO	hypercholesterolemia

Listing 13 - Study IP-001-09 : Bag accountability

Patient no.	Treatment group	Study period	Bags for the patient	Bags used by the patient
01-001	Group B	Day 0 - Day 14	28	28
		Day 14 - Day 28	28	28
01-002	Group B	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14
01-003	Group B	Day 0 - Day 14	28	28
		Day 14 - Day 28	28	28
01-004	Group A	Day 0 - Day 14	16	13
		Day 14 - Day 28	16	13
01-005	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14
01-006	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14
01-007	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14
01-008	Group B	Day 0 - Day 14	28	28
		Day 14 - Day 28	28	27
01-009	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14
01-010	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	0
01-011	Group A	Day 0 - Day 14	14	14
		Day 14 - Day 28	14	14

Listing 13 - Study IP-001-09 : Bag accountability

Patient no.	Treatment group	Study period	Bags for the patient	Bags used by the patient
05-001	Group B	Day 0 - Day 14	28	28
		Day 14 - Day 28	28	28
05-002	Group B	Day 0 - Day 14	28	28
		Day 14 - Day 28	28	21
06-001	.	Day 0 - Day 14	.	.
		Day 14 - Day 28	.	.
06-002	.	Day 0 - Day 14	.	.
		Day 14 - Day 28	.	.

Listing 14.1 - Study IP-001-09 : Serum L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	43	257	188	63	66
01-002	48	137	107	47	45
01-003	62	262	187	80	63
01-004	36	143	128	59	56
01-005	36	114	77	48	55
01-006	62	190	115	69	86
01-007	119	211	130	76	61
01-008	46	238	206	88	50
01-009	54	203	157	75	70
01-010	42	145	.	.	.
01-011	47	182	161	72	58
05-001	40	229	200	69	53
05-002	20	151	137	52	45
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 14.2 - Study IP-001-09 : Serum Acetyl-L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	5	19	35	6	7
01-002	8	30	24	11	10
01-003	8	62	66	16	11
01-004	9	25	21	9	13
01-005	11	23	12	9	8
01-006	8	14	15	5	9
01-007	19	36	31	11	7
01-008	7	17	32	10	9
01-009	7	33	28	16	10
01-010	8	37	.	.	.
01-011	7	41	39	18	9
05-001	18	79	71	20	19
05-002	8	43	42	13	10
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 15.1 - Study IP-001-09 : Urine L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	46.9	655.3	308.7	5.8	44.1
01-002	23.9	199.5	221.4	27.6	23.1
01-003	58.3	309.5	343.8	69.6	57.6
01-004	42.4	259.3	207.5	64.0	57.4
01-005	14.2	173.0	64.4	16.2	34.2
01-006	57.9	586.9	377.2	131.4	58.8
01-007	171.1	255.8	133.9	16.9	7.8
01-008	11.0	397.3	233.9	32.8	21.9
01-009	90.2	571.0	278.7	30.1	40.8
01-010	60.0	297.1	.	.	.
01-011	17.6	265.3	444.0	21.9	20.6
05-001	9.1	384.6	345.0	43.4	29.6
05-002	3.8	446.1	352.8	59.5	35.4
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 15.2 - Study IP-001-09 : Urine Acetyl-L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	10.8	190.2	72.5	2.5	66.0
01-002	10.3	123.2	101.5	9.6	7.3
01-003	20.8	199.0	124.9	23.2	15.9
01-004	4.1	59.9	66.3	13.3	18.9
01-005	6.8	65.4	13.6	4.6	12.9
01-006	14.0	148.9	121.4	35.0	17.2
01-007	83.7	124.9	84.8	7.9	2.6
01-008	4.0	126.2	85.4	13.1	9.3
01-009	25.1	196.0	96.0	14.1	16.5
01-010	-0.5	-0.5	.	.	.
01-011	8.0	103.6	181.4	9.7	8.1
05-001	3.6	141.5	139.2	19.7	16.7
05-002	1.7	138.1	138.7	22.7	14.3
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 16.1 - Study IP-001-09 : Dyalisate L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	56.4	309.8	180.1	41.2	60.2
01-002	38.3	126.5	317.9	47.1	42.7
01-003	45.2	191.5	172.2	72.9	58.6
01-004	54.4	394.7	107.2	57.0	36.3
01-005	35.1	104.6	73.6	40.8	50.7
01-006	45.6	397.8	98.7	36.8	55.9
01-007	77.9	411.1	96.4	59.4	52.6
01-008	4.7	579.9	175.7	62.0	44.4
01-009	62.3	60.3	143.1	48.7	44.5
01-010	41.8	373.1	.	.	.
01-011	23.1	537.0	147.8	39.4	37.4
05-001	40.6	229.7	196.2	68.3	54.3
05-002	15.2	196.2	148.1	42.4	43.1
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 16.2 - Study IP-001-09 : Dyalisate Acetyl-L-carnitine (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	9.6	27.6	39.9	5.4	9.0
01-002	5.3	30.5	17.6	6.6	6.3
01-003	9.4	61.4	52.6	18.7	11.3
01-004	6.9	9.2	16.4	6.8	5.3
01-005	5.4	18.6	11.0	8.3	9.4
01-006	4.6	7.9	12.0	2.3	5.7
01-007	11.7	23.1	24.6	11.2	7.6
01-008	0.6	18.0	28.2	9.7	9.2
01-009	10.0	9.3	25.1	7.5	5.3
01-010	2.7	17.0	.	.	.
01-011	2.7	18.5	32.6	6.5	5.6
05-001	15.8	67.8	64.4	16.6	15.0
05-002	2.7	30.2	43.8	9.2	7.7
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 17 - Study IP-001-09 : Oxalic acid - Oxalate (µmol/l)

Patient no.	Day 0	Day 14	Day 28	Day 42	Day 56
01-001	110.97	36.81	71.14	85.81	36.92
01-002	37.86	87.64	86.25	71.42	14.42
01-003	63.47	91.97	116.75	107.08	23.03
01-004	100.75	100.31	107.81	107.25	113.03
01-005	62.19	62.58	105.36	136.36	83.25
01-006	75.08	139.69	36.97	159.92	98.92
01-007	198.19	245.97	167.14	48.58	78.08
01-008	51.31	61.69	72.03	78.97	57.25
01-009	70.47	77.14	76.97	76.75	51.81
01-010	79.19	104.75	.	.	.
01-011	67.81	68.08	63.81	.	.
05-001	74.98	63.94	53.08	92.94	83.72
05-002	82.78	91.17	78.44	70.61	59.00
06-001	.	.	.	.	.
06-002	.	.	.	.	.

Listing 18 - Study IP-001-09 : Peritoneal equilibration test (PET) - Glucose

Patient no.	Day 0	Day 0 Not Done	Day 28	Day 28 Not done	Day 56	Day 56 Not done
01-001	0.18	No	0.23	No	0.23	No
01-002	0.29	No	0.34	No	0.26	No
01-003	0.27	No	0.30	No	0.24	No
01-004	0.31	No	0.28	No	0.37	No
01-005	0.24	No	0.22	No	0.22	No
01-006	0.27	No	0.27	No	0.31	No
01-007	0.32	No	0.27	No	0.42	No
01-008	0.34	No	0.32	No	0.34	No
01-009	0.23	No	0.28	No	0.29	No
01-010	0.73	No	.	Yes	.	Yes
01-011	0.00	No	0.31	No	0.27	No
05-001	.	Yes	.	Yes	.	Yes
05-002	.	Yes	.	Yes	.	Yes
06-001	.	Yes	.	Yes	.	Yes
06-002	.	Yes	.	Yes	.	Yes